08/920611

Docket No.: PD0586

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Berry et al.

Patent No.: 6,068,832

Issued: May 30, 2000

For: Chlorofluorocarbon-free Mometasone Furoate Aerosol Formulations

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.701-1.791, this Request is being submitted by the Applicant, Schering Corporation ("Schering") with respect to the above-identified patent, namely U.S. Patent No. 6,068,832, which matured from application Serial No. 08/920,611, having a filing date of August 27, 1997. This application claims priority from provisional application no. 60/025,807 filed on August 29, 1996. Schering is the owner of the U.S. Patent No. 6,068,832 by virtue of the Assignment to Schering from the inventors, namely, Julianne Berry, Joel A. Sequeira and Imtiaz A. Chaudry (having executed the Assignments respectively, on August 25, 1997) of each of their interests in Serial No. 08/920,611. This Assignment has been recorded in the United States Patent and Trademark Office ("USPTO") on July 27, 1998, at Reel 009344, Frame 0920 and is attached hereto as Exhibit 1. Power of Attorney granting Barry

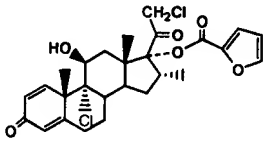
H. Jacobsen the right to act as an agent on behalf of Merck, which is the parent company of Schering Corp., is attached hereto as Exhibit 10.

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.701 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

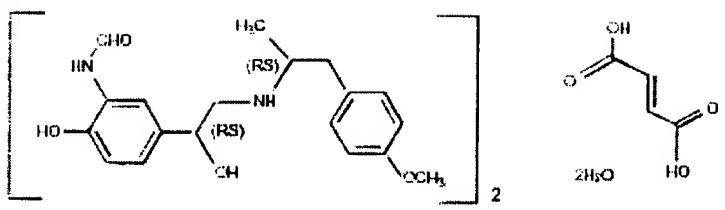
DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg, are combinations of mometasone furoate and formoterol fumarate dihydrate for oral inhalation only.

One active component of DULERA is mometasone furoate, a corticosteroid having the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) with the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight 521.44.

One active component of DULERA is formoterol fumarate dihydrate, a racemate. Formoterol fumarate dihydrate is a selective beta$_2$-adrenergic bronchodilator having the chemical name of (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate with the following chemical structure:



Formoterol fumarate dihydrate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$.

(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review for the DULERA® product occurred under Section 505(b) of the FFDCA, 21 U.S.C. § 355. Section (b) provides for the submission and approval of new drug applications ("NDAs").

(3) An identification of the date on which the product received permission of commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

The DULERA® product was approved by the FDA for commercial marketing on June 22, 2010 for the treatment of asthma in patients 12 years of age and older. See Exhibit 2 for a copy of the approval letter.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the FFDCA, The Public Health Service Act, or The Virus-Serum-Toxin Act or a statement of when the active

ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved:

The DULERA® product comprises the combination of two previously approved active ingredients, i.e., mometasone furoate and formoterol fumarate dihydrate, which should be considered as a single active ingredient under 35 U.S.C. §156 due to the synergistic effect exhibited by the combination of the active ingredients, see Exhibits 3, 4 and 5. A product with the combination has not been previously approved under Section 505(b) of the FFDCA. No other combination containing these two active ingredients has been approved for commercial marketing or use under FFDCA, the Public Health Service Act. or the Virus-Serum-Toxin Act.

The active ingredient mometasone furoate, was previously approved for commercial marketing on April 30, 1987, in connection with approval under under Section 505 of the FFDCA [21 U.S.C. §355] for the commercial marketing of ELOCON® Ointment, which contains mometasone furoate as its active ingredient, for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Mometasone furoate monohydrate was approved for commercial marketing on October 1, 1997, in connection with approval under under Section 505 of the FFDCA [21 U.S.C. §355] for the commercial marketing of NASONEX® Nasal Spray, for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis, and for the treatment of nasal polyps.

The active ingredient mometasone furoate, was approved for commercial marketing on March 30, 2005, in connection with approval under under Section 505 of the FFDCA [21 U.S.C. §355] for the commercial marketing of the ASMANEX® TWISTHALER® product for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older, and also for asthma patients who require oral corticosteroid therapy, where adding

ASMANEX® TWISTHALER® therapy may reduce or eliminate the need for oral corticosteroids.

The active ingredient formoterol fumarate dihydrate, was previously approved for commercial marketing on Feb 16, 2001, in connection with approval under under Section 505 of the FFDCA for the commercial marketing of FORADIL AEROLIZER ®. FORADIL AEROLIZER ® is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma. FORADIL AEROLIZER ® is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis. FORADIL AEROLIZER ® is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Sec. 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The DULERA® product was approved on June 22, 2010, and the last day within the sixty day period permitted for submission of an application for extension of the relevant U.S. Patent is August 20, 2010. This application is being timely filed on August 19, 2010, before the expiration of the August 20, 2010 deadline.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

UNITED STATES PATENT NO.: 6,068,832

INVENTORS: Berry, Et Al.

DATE OF ISSUE: May 30, 2000

EXPIRATION DATE: August 27, 2017

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings::

A copy of U.S. Patent No. 6,068,832 is attached as Exhibit 6.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

No terminal disclaimers were filed for U.S. Patent No. 6,068,832. United States Patent No. 6,068,832 has not been re-examined and, as such, no re-examination certificate has been issued. No certificates of correction have been filed for U.S. Patent No. 6,068,832. The first and second maintenance fee for U.S. Patent No. 6,068,832 was timely paid as shown by the USPTO Maintenance Fee Statements found in Exhibit 7, respectively.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least on such patent claim reads on:

(i) the approved product, if the listed claims include any claim to the approved product;

(ii) the method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) the method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product:

U.S. Patent No. 6,068,832 reads on the approved DULERA® product, either literally or under the doctrine of equivalents. Specifically, at least claims 1-14 read on the approved DULERA® product literally or under the doctrine of equivalents. The entire label for the DULERA® product can be found in Exhibit 8.

Claim 1 of U.S. Patent No. 6,068,832 reads as follows:

1. An aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane, about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

Applicant submits that claim 1 covers the DULERA® for the following reasons:

1) The first part of Claim 1 reads:

An aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane,

- As per the label for the DULERA® product, the DULERA product includes an aerosol suspension formulation comprising 1,1,1,2,3,3,3-heptafluoropropane (e.g. hydrofluoroalkane (HFA-227) in propelled pressurized metered dose inhaler.

2) The second part of Claim 1 reads:

about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the

ethanol concentration, the formulation optionally also containing a surfactant.

- As per the label, the DULERA® product contains anhydrous alcohol as a cosolvent and oleic acid as a surfactant. Applicant submits that the ethanol is present in a weight percent between about 1 and about 10 percent. Applicant submits that the mometasone furoate is micronized and that the mometasone furoate is in a concentration of at least 1 percent of the ethanol concentration. The DULERA® product does contain a surfactant.

Claim 8 of U.S. Patent No. 6,068,832 reads as follows:

8. A method for treating allergic reactions in the respiratory tract, comprising administering by inhalation an aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane, about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

Applicant submits that claim 8 covers the DULERA® for the following reasons:

1) The first part of Claim 8 reads:

A method for treating allergic reactions in the respiratory tract

- As per the label, the DULERA® product is indicated for the treatment of asthma in patients 12 years of age and older. As per the specification of US 6,068,832, "formulations of the present invention which are suitable for treating lower respiratory system disorders such as asthma", see col. 3, lines 8-10. As per the label, the DULERA® product was approved for the treatment of asthma in patients 12 years of age and older. Applicants submit that asthma may be caused by an allergic reaction.

2) The second part of Claim 8 reads:

comprising administering by inhalation an aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane,

- As per the label for the DULERA® product, the DULERA product includes an aerosol suspension formulation comprising 1,1,1,2,3,3,3-heptafluoropropane (e.g. hydrofluoroalkane (HFA-227) in propelled pressurized metered dose inhaler.

3) The third part of Claim 8 reads:

about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

- As per the label, the DULERA® product contains anhydrous alcohol as a cosolvent and oleic acid as a surfactant. Applicant submits that the ethanol is present in a weight percent between about 1 and about 10 percent. Applicant submits that the mometasone furoate is micronized and that the mometasone furoate is in a concentration of at least 1 percent of the ethanol concentration. The DULERA® product does contain a surfactant.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the Investigational New Drug (IND) application and the IND Number; the date on which a New Drug Application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and the date on which the NDA was approved or the Product License issued:

On May 26, 2006, Schering submitted to the FDA an "Investigational New Drug Application" for DULERA® under Section 505 of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent NDA for the use of the DULERA® product. The FDA received the IND on May 30, 2006. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) as June 29, 2006, the effective date of an investigational exemption, which is 30 days after the FDA received the Investigational New Drug Application. (See 21 C.F.R. §312.40(b).)

On May 22, 2009, Schering submitted to the FDA an original NDA for the DULERA® product. On June 22, 2010, FDA approved NDA 22-5518 the DULERA® product. See Exhibit 2.

(11) A brief description beginning on a new page of the significant activities undertaken by Schering, the marketing applicant, during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

Please see attached Exhibit 9 for a chart that provides the chronology of significant activities undertaken by Schering during the regulatory review period.

(12) A statement beginning on a new page that in the opinion of the Applicant, the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(A)Statement as to eligibility of extension:

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

Applicant believes that U.S. Patent No. 6,068,832 is eligible for extension under 35 U.S.C. §156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C 156(a)

U.S. Patent No. 6,068,832 claims a product and the method of using a product (35 U.S.C. §156(a)).

(2) 35 U.S.C 156(a) (1)

Pursuant to the relevant version of 35 U.S.C. §154 applicable to U.S. Patent No. 6,068,832and 35 U.S.C. §156, the term of U.S. Patent No. 6,068,832 is currently set to expire on August 27, 2017. This application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. 6,068,832.

(3) 35 U.S.C 156(a) (2)

The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(4) 35 U.S.C 156(a) (3)

The application for extension is submitted by the owner of record in accordance with the requirement under 35 U.S.C. §156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C 156(a) (4)

As evidenced by the June 22, 2010 letter from the FDA (Exhibit 2), to Schering Corporation, the product was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(6) 35 U.S.C 156(c) (4)

The commercial marketing and use of the DULERA® product is the first permitted commercial and marketing or use of a product with the

combination of mometasone furoate and formoterol fumarate dihydrate under Section 505 of the FFDCA 21 U.S.C. §355. The combination of mometasone furoate and formoterol fumarate dihydrate should be considered as a single active ingredient under the statue in that it has substantial differences as compared to use of those same compounds alone. A discussion of the synergistic effects can be found in Exhibits 3, 4 and 5.

(B)Statement as to length of extension:

The length of the extension of the patent term for US Patent No. 6,068,832 claimed by the Applicant is 926 days. The length of extension was determined pursuant to 37 C.F.R. 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. §156(g)(1), which began on June 29, 2006 and ended on June 22, 2010, which is a total of 1,455 days which is the sum of (a) and (b) below:

(a) The testing period of review (IND 70,283) under 35 U.S.C. §156(g)(1)(B)(i) began on June 29, 2006 and ended on May 21, 2009, which is a total of 1058 days.

(b) The approval period of review (NDA 22-518) under 35 U.S.C. §156(g)(1) (B)(ii) began on May 22, 2009 and ended on June 22, 2010, which is 397 days;

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub paragraph (12)(B)(a) above (1,474) less

(a) the number of days in the regulatory review period which were on or before the date on which the patent issued is 0 since the IND acceptance date was after the issuance of the patent;

(b) the number of days during which the Applicant did not act with due diligence which is zero (0) days, and

(c) one-half the number of days determined in subparagraph 12(B)(1)(a) after the patent issued [(1,058/2] or which is 529 days

(d) The regulatory period is calculated by subtracting the number of days determined in subparagraph 12(B)2)(a)-(c) from the entire regulatory review period as determined in subparagraph 12(B)(1) which is 1,455-0-0-529 which equals 926 days.

(3) The number of days as determined in subparagraph 12(B)(2)(d) or 926 days when added to the original term of the patent would result in the date of March 10, 2020.

(4) Fourteen (14) years when added to the date of NDA Approval (June 22, 2010) is June 24, 2024;

(5) The earlier date as determined in subparagraphs (3) and (4) is March 10, 2020;

(6) Since the original patent issued was not issued before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, five (5) years when added to the original expiration date of the patent (August 27, 2017) would result in the date of August 27, 2022;

(7) the earlier date as determined in subparagraph 12(B)(5) and (6) is March 10, 2020. Accordingly, United States Patent No. 6,068,832 is eligible for a patent term extension from August 27, 2017 to March 10, 2020.

(13) A statement that Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (SEE 37 C.F.R. §1.765).

Schering acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (SEE 37 C.F.R. §1.20(J)):

The Director is hereby authorized to charge our Deposit Account No. 19-0365 in the amount of **$1,120.00**. The Director is also hereby authorized to charge our Deposit Account, 19-0365 with respect to any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Barry Jacobsen, Esq.
Merck
2000 Galloping Hill Road
Kenilworth, NJ 07033
Telephone No.: (908) 298-5056
Facsimile No.: (908) 298-5388

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156 is accompanied by two additional copies of the Request, for a total submission of three copies.

The undersigned is authorized to act on behalf of the Applicant, Schering Corporation, by virtue of the executed Statement Under 37 C.F.R. 3.73(b) and the executed Power of Attorney and Correspondence Address Indication Form, both of which are attached to the original Request.

Dated: August 19, 2010

Respectfully submitted,

By Barry H. Jacobsen

Barry H. Jacobsen
Registration No.: 43,689
Merck
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 298-5056
Attorney for Applicant

EXHIBIT 1

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6068832 **Issue Dt:** 05/30/2000 **Application #:** 08920611 **Filing Dt:** 08/27/1997

Inventors: JULIANNE BERRY, JOEL A. SEQUEIRA, IMTIAZ A. CHAUDRY

Title: CHLOROFLUOROCARBON-FREE MOMETASONE FUROATE AEROSOL FORMULATIONS

Assignment: 1

Reel/Frame: 009344/0920 **Recorded:** 07/27/1998 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: BERRY, JULIANNE **Exec Dt:** 08/25/1997

SEQUEIRA, JOEL A. **Exec Dt:** 08/25/1997

CHAUDRY, IMTIAZ A. **Exec Dt:** 08/25/1997

Assignee: SCHERING CORPORATION
2000 GALLOPING HILL ROAD
KENILWORTH, NEW JERSEY 07033

Correspondent: SCHERING-PLOUGH CORPORATION
ROBERT A. FRANKS
PATENT DEPARTMENT, K-6-1 1990
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

Search Results as of: 08/15/2010 03:53 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.2

EXHIBIT 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-518

NDA APPROVAL

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Attention: Michael Belman
Director & Liasion, Global Regulatory Affairs

Dear Mr. Belman:

Please refer to your New Drug Application (NDA) dated May 21, 2009, received May 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol 100/5 and 200/5 micrograms.

We acknowledge receipt of your submissions dated June 4 and 16, July 1, 16 and 24, August 12 and 26, September 4 and 22, October 29 and November 4, 10, 13 and 25, 2009, January 11, 14, 22 and 29, February 3, 12 and 16, March 5 and 16, May 21 and 26 and June 10, 11, 15, 18, 21 and 22, 2010.

This new drug application provides for the use of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol for the treatment of asthma, in adults and children 12 years of age and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, submitted June 22, 2010 and Medication Guide, submitted June 22, 2010. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on June 18, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-518.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Your application for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol was not referred to an FDA advisory committee. The use of an inhaled corticosteroid and long-acting beta agonist (LABA) in combination are well established for the treatment of asthma and Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol combines two active ingredients that are individually well studied in other formulations and devices in patients with asthma. Therefore, this application did not warrant discussion at an advisory committee meeting.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. The role of LABAs in asthma therapy for patients 4 years of age and younger is not established.

We are deferring submission of your pediatric studies for ages 5 to 11 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. In addition, you are attempting to develop an additional low strength formulation with an assessment for patients 5 to 11 years of age.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of the postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

1658-1 Deferred pediatric trial under PREA to compare the pharmacodynamics of DULERA with and without a spacer in children 5 to 11 years of age

Protocol Submission:	October 2010
Study Completion:	February 2012
Final Report Submission:	July 2012

1658-2 Deferred pediatric trial under PREA to compare the pharmacokinetics of DULERA with and without a spacer in children 5 to 11 years of age

Protocol Submission:	July 2012
Study Completion:	June 2014
Final Report Submission:	November 2014

1658-3 Deferred pediatric trial under PREA to evaluate the effects of DULERA on the HPA axis in children 5 to 11 years of age. In lieu of an HPA axis study, you may provide robust data to demonstrate that the systemic exposure of mometasone from DULERA is comparable or lower than that from the mometasone dry powder inhaler.

Protocol Submission:	May 2012
Study Completion:	October 2013
Final Report Submission:	March 2014

1658-4 Deferred pediatric trial under PREA to evaluate the safety and efficacy of multiple doses of mometasone MDI in children 5 to 11 years of age with asthma.

Protocol Submission:	April 2012
Study Completion:	March 2014
Final Report Submission:	August 2014

1658-5 Deferred pediatric trial under PREA to evaluate the safety and efficacy of DULERA compared to mometasone MDI in children 5 to 11 years of age with asthma. This study will be 12- 26 weeks duration.

Protocol Submission:	May 2014
Study Completion:	August 2016
Final Report Submission:	January 2017

1658-6 Deferred pediatric trial under PREA to evaluate the long-term safety of DULERA in children 5 to 11 years of age with asthma. This study will be 26 weeks duration with a 6 month extension

Protocol Submission:	July 2014
Study Completion:	October 2016
Final Report Submission:	March 2017

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to evaluate the risk of serious asthma outcomes (asthma related death, intubations, and hospitalizations) with the use of a long-acting beta agonist (LABA), included Dulera (mometasone and formoterol fumarate).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess serious asthma outcomes (asthma related death, intubations, and hospitalizations) with the use of a LABA.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct one or more postmarketing clinical trials with Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol compared to inhaled corticosteroids in adults and adolescent patients with asthma, to evaluate the risk of serious asthma outcomes. Submit a proposal to address this requirement.

Submit the proposal to your IND, with a cross-reference letter to this NDA 22-518. Submit all final report(s) to your NDA 22-518. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Post-approval Agreements

We remind you of our agreements from your submissions dated November 25, 2009, January 14, 2010, and March 5, 2010, listed below:

1. Cirrus Pharmaceuticals Inc. (Research Triangle Park, NC 27709, USA) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227.

2. Re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data.

3. Introduce methodology identical or equivalent/better than that contained within USP-NF General Chapter <401> for control of fatty acid composition in oleic acid.

4. Re -evaluate the drug product specifications for APSD and the drug product specifications for degradation products "using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data.

5. Maintain specifications (i.e., a list of tests, the acceptance criteria and the test methods) in NDA 22-518 for each of the two drug substances.

6. Investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and report the progress and submit results to the Agency within 6 months of the date of the information request, dated February 19, 2010.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our REMS notification letter dated February 18, 2010.

Your proposed REMS, submitted on June 22, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

i. An evaluation of patients' understanding of the serious risks of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, including the increased risk of asthma-related deaths.

ii. An analysis of prescribers' understanding of the increased risk of asthma-related deaths and the safe use of LABAs.

iii. A description of specific measures that would be taken to increase awareness if the assessment of healthcare prescribers indicates that prescriber awareness is not adequate.

iv. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.

v. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)

vi. With regard to the communication plan:

1. The date of launch of the communication plan (DHCP letter, website, and communication to professional societies)
2. The number of recipients of the DCHP letter distribution
3. Date(s) of distribution of the DHCP letter
4. A copy of all documents included in each distribution
5. The professional societies to which you communicated
6. The information that the professional societies disseminated to its members and the timing for the dissemination

vii. Based on the information reported, an assessment of and conclusion regarding whether the REMS is meeting its goal and whether modifications to the REMS are needed.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-518
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-518
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-518
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Eunice Chung, Regulatory Project Manager, at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

EXHIBIT 3

Case 4-30843D/HO 16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
IAN FRANCIS HASSAN ET AL
APPLICATION NO: 10/718,316
FILED: November 20, 2003
FOR: COMBINATIONS OF FORMOTEROL AND MOMETASONE FUROATE FOR ASTHMA

Group Art Unit: 1617
Examiner: HUI, SAN MING R

DECLARATION UNDER RULE 132

I, Alexandre Trifilieff, a citizen of France, declare:

1. I am a graduate of the University of Provence, Marseille, France, where I was awarded the degree of Bachelor of Science in Biochemistry in 1989. I was awarded the degree of Master of Science in Pharmacology in 1990 and the degree of Doctor of Philosophy (PhD) in Pharmacology in 1993 by the University Louis Pasteur, Strasbourg, France, my thesis being entitled "Kinins airway receptors".

I was a Post-Doctoral Fellow at the University of Southampton, United Kingdom, from 1993 to 1995, specialising in cell culture and immunohistochemistry techniques on bronchial biopsies and cultured epithelial cells, particularly with respect to their application to the characterization of inflammatory cells and adhesion molecules in asthma. I was a Post-Doctoral Fellow in the Respiratory Disease Department of Ciba-Geigy AG, Basel, Switzerland, from 1995 to 1997, specialising in the development of *in vivo* murine models of asthma, immunohistochemistry and morphometric studies on lung tissues and cultured pulmonary cells, and primary culture of pulmonary smooth muscle and epithelial cells, particularly with respect to their application to the characterization of inflammatory reactions and the remodelling process in the airway.

Since June 1997, I have held the position of Biology Laboratory Head in the Horsham Research Centre of Novartis Pharmaceuticals UK Limited, and have been leader or co-leader of various pre-clinical programs, specialising in the development of *in vivo* models of lung inflammation.

I am the co-author of 34 scientific papers on inflammation and related pharmacology, particularly of the airways, which have been published in scientific journals of high standards, such as Journal of Immunology, European Journal of Pharmacology, British Journal of Pharmacology, Journal of Clinical Investigation and American Journal of Respiratory and Critical Care Medicine.

2. The following tests were carried out under my supervision:

The comparative effects of formoterol, mometasone furoate and a combination of formoterol and mometasone furoate on lung function following antigen challenge were studied in immunised 6 week- old female BALB/c mice obtained from Charles River (Margate, UK). All experiments conformed to the UK Animals (Scientific Procedures) Act 1986.

The mice were immunised intraperitoneally on day 0 and day 14 with 20μg of ovalbumin (grade V, Sigma, Poole, UK) in 0.1ml of alum (Serva, Heidelberg, Germany). On days 21, 22 and 23, the mice were exposed, for 20 minutes, to an aerosol of 1 % ovalbumin in phosphate buffered saline (PBS). On day 26, the baseline airway responsiveness of each animal was measured for 5 minutes using whole body plethysmography and enhanced pause (Penh) values determined following the procedure of E. Hamelmann et al, Am J Respir Crit Care, Vol. 156, pp. 766-775, 1997, and then, in a final antigen challenge, the mice were exposed, for 20 minutes, to an aerosol of 5% ovalbumin in PBS or PBS alone.

One hour after the last challenge, different groups of the ovalbumin-challenged mice were treated intranasally with solutions of 50μl PBS containing respectively 1) 2% N-methyl-pyrrolidone (Control), 2) formoterol fumarate dihydrate in 2% N-methylpyrrolidone, 3) mometasone furoate in 2% N-methylpyrrolidone, and 4) formoterol fumarate dihydrate and mometasone furoate in 2% N-methylpyrrolidone. The doses of formoterol fumarate dihydrate and mometasone furoate used in solutions 2), 3) and 4) are given under Results below. The doses of 15 microg/kg formoterol fumarate dihydrate alone and 300 microg/kg

mometasone furoate alone were used only in order to assist in the plotting of dose response curves. Four hours after the last antigen challenge, the airway responsiveness of each animal was measured again as previously for 5 minutes using whole body plethysmography and the Penh values determined. The ratio of the Penh value post antigen challenge to the baseline Penh value was recorded for each of the animals. The increases in Penh values after antigen challenge are a measure of the bronchoconstriction resulting from the challenge. Dose response curves were plotted for the Penh post antigen : baseline ratio.

3. The experimental data were analysed as follows :

The possible synergistic interaction between the two compounds was analyzed by the algebraic method developed by Berenbaum (M C Berenbaum, *Clinical and Experimental Immunology 28, 1-18* (1977). Based on experimental data, the following coefficient, the "Berenbaum coefficient", was calculated:

M/Me + F/Fe

where M and F are the doses of mometasone furoate and formoterol fumarate dihydrate respectively, given in combination, that achieve a given quantitative effect; and

Me and Fe are the doses of mometasone furoate and formoterol fumarate dihydrate respectively, given alone, that produce the same quantitative effect, i.e. ratio of Penh post antigen to Penh baseline (equi-effective dose, obtained by extrapolation of the Penh ratio dose response curve for each entity).

A coefficient of 1 indicates an additive effect, a coefficient of less than one a synergistic effect and a coefficient greater than 1 an antagonistic effect, between the two compounds.

Results were expressed as means ± standard error of the mean.

4. The results of the above tests and my conclusions therefrom are as follows:

Results

The determined Penh values for various doses of formoterol fumarate dihydrate, mometasone furoate and a combination of the two are given in the following table:

Penh values

			Formoterol (microg/kg)			
			0	1	5	15
Mometasone (microg/kg)	0	Baseline	163 ± 7	165 ± 8	161 ± 5	168 ± 9
		+4hrs	564 ± 77	545 ± 59	388 ± 63	302 ± 47
	10	Baseline	197 ± 4	180 ± 4	169 ± 8	
		+4hrs	621 ± 75	452 ± 50	307 ± 27	
	100	Baseline	157 ± 5	172 ± 8	172 ± 9	
		+4hrs	492 ± 84	304 ± 50	239 ± 37	
	300	Baseline	173 ± 7			
		+4hrs	406 ± 41			

The ratios of the Penh value post antigen challenge to the baseline Penh value for various doses of formoterol fumarate dihydrate, mometasone furoate and a combination of the two were as shown in the following table:

Ratios of the Penh value post antigen challenge to the baseline Penh value

		Formoterol (microg/kg)			
		0	1	5	15
Mometasone (microg/kg)	0	3.43	3.36	2.42	1.79
	10	3.15	2.5	1.84	
	100	3.11	1.77	1.41	
	300	2.57			

For the four combinations of formoterol and mometasone shown in the above table, the values of F, M, Fe and Me for calculation of the Berenbaum coefficient are shown in the following table together with the ratios of the measured Penh values, Fe and Me being obtained by extrapolation of the dose response curves for formoterol and mometasone respectively. The resulting Berenbaum coefficients for the combinations are also shown.

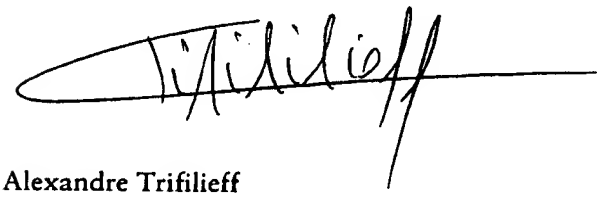
F (microg/kg)	M (microg/kg)	Penh ratio	Fe (microg/kg)	Me (microg/kg)	Berenbaum coefficient
1	10	2.5	4.9	366.6	0.23
5	10	1.84	11.5	736.6	0.45
1	100	1.77	11.8	738.7	0.22
5	100	1.41	23.8	987.8	0.31

Conclusions

The results show that the combination of formoterol fumarate dihydrate and mometasone furoate gives a considerable synergistic improvement in lung function compared with the sum of the effects of an equi-effective dose of formoterol fumarate dihydrate alone and an equi-effective dose of mometasone furoate alone, irrespective of the actual doses used. This synergistic effect has been clearly shown shown for a wide range of ratios of formoterol dose to mometasone dose, from 1:2 to 1:100.

4. I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signed this day of 16th of September 2004



Alexandre Trifilieff

EXHIBIT 4

Case 4-30843B/C1/HO 16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
IAN FRANCIS HASSAN ET AL
APPLICATION NO: 09/942,805
FILED: AUGUST 30,2001
FOR: COMBINATIONS OF FORMOTEROL AND MOMETASONE FUROATE FOR ASTHMA

Group Art Unit: 1617
Examiner: HUI, SAN MING R

DECLARATION UNDER RULE 132

I, Claudia Zuany Amorim Fromond, a citizen of Brazil permanently residing at 12, Abbotsbury Court, Horsham, West Sussex, RH13 5PT, United Kingdom, declare:

1. I am a graduate of the University of Estado do Rio de Janiero, Brazil, where I was awarded the degree of Bachelor of Science in Pharmacology in 1986, and was awarded the degree of Doctor of Philosophy (PhD) in Cellular and Molecular Biology at Oswaldo Cruz Foundation, by the Conselho Nacional de Pesquisa (CNPq), Brazil in 1993, my thesis being entitled "Characterisation of different inflammatory allergic models in actively sensitised mice".

I joined the Horsham Research Centre of Novartis Pharmaceuticals UK Limited in April 1998 and since September 1999 have held the position of Project Leader for Vaccination/ Immunotherapy for allergic diseases.

I am the co-author of 22 scientific papers on inflammation and related pharmacology, particularly of the airways, which have been published in scientific journals of high standards, such as Science, Journal of Clinical Investigation, Journal of Immunology, European Journal of Immunology and British Journal of Pharmacology.

2. The following tests were carried out under my supervision:

The comparative effects of formoterol, mometasone furoate and a combination of formoterol and mometasone furoate on antigen-induced eosinophilia were studied in immunised BALB/c mice. Male BALB/c mice approximately 7 weeks old were immunised intraperitoneally with 0.9% w/v saline (0.2ml) containing 100μg of ovalbumin (5 times crystallised, Sigma, UK) adsorbed in 1.6mg of aluminium hydroxide (Sigma). Ten days after immunisation, the mice were challenged four times, once a day, with ovalbumin (20μg) in phosphate buffered saline (PBS, 50μl), delivered intranasally. Control animals were similarly immunised with ovalbumin and challenged intranasally with PBS (50μl).

12 hours after the last intranasal challenge, different groups of the ovalbumin-challenged mice were intranasally treated with 50μl saline containing respectively 1) 2% DMSO, 2) formoterol fumarate dihydrate (1.5μg/kg) and 2% DMSO, 3) mometasone furoate (30μg/kg) and 2% DMSO and 4) formoterol fumarate dihydrate (1.5μg/kg), mometasone furoate (30μg/kg) and 2% DMSO. The doses of formoterol and mometasone furoate were selected to reflect the ratio of clinical doses of these compounds.

24 hours after the last intranasal ovalbumin or PBS challenge, all of the mice were anaesthetised by an intraperitoneal injection of sodium pentobarbital (4mg/kg). Bronchoalveolar lavage (BAL) fluid was collected by cannulating the trachea and washing the lungs with saline (3 x 0.4ml). Total cell count was determined and cytopsin preparation (Shandon Scientific Limited, UK) performed. Cells were stained with Diff-Quik (Baxter Dade AG, Switzerland) and a differential count of 200 cells was performed using standard morphological criteria to determine the level of eosinophils in the BAL fluid. The results were expressed as percentage of eosinophil numbers in the ovalbumin-challenged, DMSO vehicle-treated control.

3. The results of the above tests and my conclusion therefrom are as follows:

Results

The intranasal administration of 20μg ovalbumin to immunised mice induced an increase in eosinophil numbers in the BAL fluid at 24 hours after the last intranasal ovalbumin challenge, compared to the control challenged only with PBS (from $0.03 \pm 0.01 \times 10^5$ cells/ml to $3.69 \pm 0.39 \times 10^5$ cells/ml). The administration of formoterol fumarate dihydrate reduced eosinophil levels in the BAL fluid by 30% (significance $P<0.03$). On the administration of mometasone

furoate, no inhibitory effect on eosinophil levels was observed. The administration of formoterol fumarate dihydrate together with mometasone furoate reduced eosinophil levels in the BAL fluid by 48% (significance P<0.006).

Conclusion

From the above results, I conclude that the combination of formoterol and mometasone furoate has an anti-inflammatory effect in a conventional in vivo model of inflammation in airways diseases which is 60% greater than the sum of the effects of formoterol alone and mometasone furoate alone, i.e. a synergistic anti-inflammatory effect.

4. I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signed this 26 day of February 2002

Claudia Zuany Amorim Fromond

EXHIBIT 5

British Journal of Pharmacology (2007) 152, 83–90

0007–1188/07 $30.00
www.brjpharmacol.org

RESEARCH PAPER

Synergistic effect of formoterol and mometasone in a mouse model of allergic lung inflammation

D Wyss[1], O Bonneau[2] and A Trifilieff[1]

[1]*Novartis Institute for BioMedical Research, Respiratory Diseases Area, Basel, Switzerland and* [2]*Novartis Institute for BioMedical Research, Respiratory Diseases Area, Horsham, UK*

Background and purpose: Controversy still exists as to whether or not inhaled β_2-adrenoceptor agonists and corticosteroids act synergistically *in vivo*. In this study, we have used a murine model of lung inflammation to study the synergistic effect of an inhaled β_2-adrenoceptor agonists (formoterol) and an inhaled corticosteroid (mometasone).
Experimental approach: Actively sensitized mice were challenged with aerosolized ovalbumin, once a day, for three consecutive days. Three days after the last of the three challenges, a final allergen challenge was given. Allergen-induced increase in Penh was measured 4 h after the last challenge. A day after the last challenge, increased airway sensitivity to aerosolized methacholine was demonstrated and this was concomitant with an influx of inflammatory cells in the bronchoalveolar lavage fluids.
Key results: Mometasone (0.1 to 3 mg kg^{-1}) given intranasally either an hour before or after the last allergen challenge, dose-dependently inhibited all parameters. When given intranasally either one or three hours after the last allergen challenge, but not an hour before, formoterol (1.5 to 150 μg kg^{-1}) also dose-dependently inhibited most of the parameters to different degree. A synergistic effect on the allergen-induced increase in Penh was demonstrated for mometasone and formoterol given in combination, an hour after the challenge, at the following doses: mometasone/formoterol (in μg kg^{-1}) 1/10, 1/100, 5/10, and 5/100.
Conclusions and implications: Our results support the hypothesis that when given as a fixed combination, inhaled corticosteroid and β_2-adrenoceptor agonist act synergistically *in vivo*.
British Journal of Pharmacology (2007) **152**, 83–90; doi:10.1038/sj.bjp.0707381; published online 9 July 2007

Keywords: asthma; corticosteroids; β_2-adrenoceptor agonists; combination

Abbreviations: BAL, bronchoalveolar lavage; OA, ovalbumin; PBS, phosphate-buffered saline; PC_{200}, concentration of methacholine that produced a 200% increase above baseline of the Penh value

Introduction

Asthma is characterized by chronic inflammation of the airway with variable airflow limitation resulting in recurrent wheezing, chest tightness and cough. Inhaled β_2-adrenoceptor agonists and inhaled corticosteroids are the most effective therapies available for asthma management. Activation of the transmembrane β_2-adrenoceptor leads to an increase in intracellular cAMP, which in turn promotes relaxation of the airway smooth muscle cells. On the other hand, upon activation, the intracellular corticosteroid receptor can either downregulate pro-inflammatory gene transcription or upregulate anti-inflammatory genes. Therefore inhaled β_2 agonists act as bronchodilator agents whereas inhaled corticosteroids downregulate the inflammatory reaction within the lungs of asthmatic patients.

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Received 25 April 2007; revised 22 May 2007; accepted 7 June 2007; published online 9 July 2007

Many clinical studies have demonstrated that the use of fixed-dose combinations provides better asthma control than increasing the dose of steroid alone. This has led to the recent introduction of fixed-dose combination inhalers containing both a β_2-adrenoceptor agonist and a corticosteroid (Nelson, 2001; Kuna and Kuprys, 2002). Recent *in vitro* evidence suggests that in addition to their complementary beneficial effects (that is bronchial relaxation and anti-inflammatory activities), these two classes of drugs might have several positive interactions that could be of clinical relevance and lead to a synergistic effect when given as a fixed-dose combination to the patients (Nelson *et al.*, 2003). Although a positive interaction between these two classes of drugs has been demonstrated in a model of acetaldehyde-induced airway responses in the anaesthetized guinea-pig (Rossoni *et al.*, 2005), evidence for a true synergistic effect in conscious animals using a more relevant model of asthma has not yet been demonstrated. Hence, it is still a matter of debate as to whether the beneficial effect of a fixed-dose

combination in asthma is due to an additive or a synergistic effect (Lipworth and Fardon, 2004; Metcalfe and Moodie, 2004). In this study, we have used a previously described allergen-driven model of pulmonary inflammation in mice (Cieslewicz *et al.*, 1999; Bonneau *et al.*, 2006) to study the potential synergistic effect of an inhaled β_2-adrenoceptor agonists (formoterol) and an inhaled corticosteroid (mometasone), using the algebraic method developed by Berenbaum (1977). Our results support the hypothesis that, when given as a fixed combination, an inhaled corticosteroid and β_2-adrenoceptor agonist act synergistically *in vivo*.

Methods

Animals

Female BALB/c mice (11 weeks old, Charles River, UK) were housed in plastic cages in an air-conditioned room at 24°C in a 12 h light–dark cycle. All animals were acclimatized in the animal unit for at least 7 days before the start of any experimental work. Food and water were available *ad libitum*. The studies described here were carried out in the UK and conformed to the United Kingdom Animal (scientific procedures) Act 1986. A total of 340 animals were used for the study.

Sensitization and challenge

Mice were immunized i.p. with 20 μg of ovalbumin (OA) in 0.1 ml of Alum (Serva, Heidelberg, Germany) on days 0 and 14. On days 21–23, animals were exposed, for 20 min, to an aerosol of OA (10 mg ml^{-1}) in phosphate-buffered saline (PBS), to establish the inflammatory process within the lung, or PBS alone as a control. On day 26, a final challenge was given as an aerosol solution of OA in PBS (50 mg ml^{-1}) or PBS alone for 20 min (Bonneau *et al.*, 2006).

Lung function measurements

All lung function measurements were done using whole body plethysmography, using enhanced pause (Penh) as a read out, in conscious animals and expressed as area under the curve measured for 5 min (Bonneau *et al.*, 2006).

On day 26, before the last allergen challenge, baseline Penh measurements were taken for each animal and again 4 h after the last challenge. Airway reactivity to aerosolized methacholine (0–0.6 M) was measured, in a cumulative fashion, 1 day after the last challenge.

Bronchoalveolar lavage

Two days after the last allergen challenge and following the measurement of allergen-induced increase in Penh and airway reactivity to methacholine, the animals were killed by an i.p. injection of 60 mg kg^{-1} pentobarbitone and bronchoalveolar lavage (BAL) was performed, by injecting four times 0.3 ml of PBS into the airway lumen, for determination of inflammatory cells numbers (Bonneau *et al.*, 2006).

Drug treatment

Formoterol, mometasone or their combination were given, intranasally, as a solution in 50 μl of PBS containing 2% *N*-methyl pyronidole (Bonneau *et al.*, 2006).

Data analysis

Results are expressed as means ± s.e.mean. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons and a *P*-value of less than 0.05 was considered significant (Systat V.10.2).

For comparison of the airway reactivity to aerosolized methacholine between groups, a sigmoidal curve was fitted to the dose–response data and used to calculate the concentration of methacholine that produced a 200% increase (PC_{200}) above baseline of the Penh value (Origin V. 7.0).

The possible synergistic interaction between the two compounds was analysed by the algebraic method developed by Berenbaum (1977). On the basis of experimental data, the following coefficient was calculated: M/Me + F/Fe. M and F are the dose of mometasone and formoterol, given in combination that achieve a given quantitative effect. Me and Fe are the dose of mometasone and formoterol, given alone, that produce the same quantitative effect (equieffective dose). A coefficient of 1 would indicate an additive effect, less than 1 a synergistic effect and greater than 1 an antagonistic effect, for the two compounds.

Drugs

Formoterol and mometasone were synthesized at the Research Department of Novartis Pharma. All other reagents were purchased from Sigma-Aldrich (Poole, UK) unless specified otherwise.

Results

Three control groups were used in the following studies: a negative control group refers to sensitized animals challenged with PBS on days 21–23 and 26 (PBS/PBS). A baseline control group refers to sensitized animals challenged with OA on days 21–23 and challenged with PBS on day 26 (PBS/OA). A positive control group refers to sensitized animals challenged with OA on days 21–23 and 26 (OA/OA).

Effect of mometasone given an hour before the last allergen challenge

When compared with the PBS/PBS or the OA/PBS group, the OA/OA group developed an increase in Penh 4 h after the last challenge (Figure 1a). The allergen-induced increase in Penh in the OA/OA group was dose-dependently inhibited by mometasone, given an hour before the last allergen challenge, and a full inhibition was observed at a dose of 0.3 mg kg^{-1} (Figure 1a). When compared with the PBS/PBS and the OA/PBS groups, the OA/OA group was hypersensitive to aerosolized methacholine as demonstrated by a

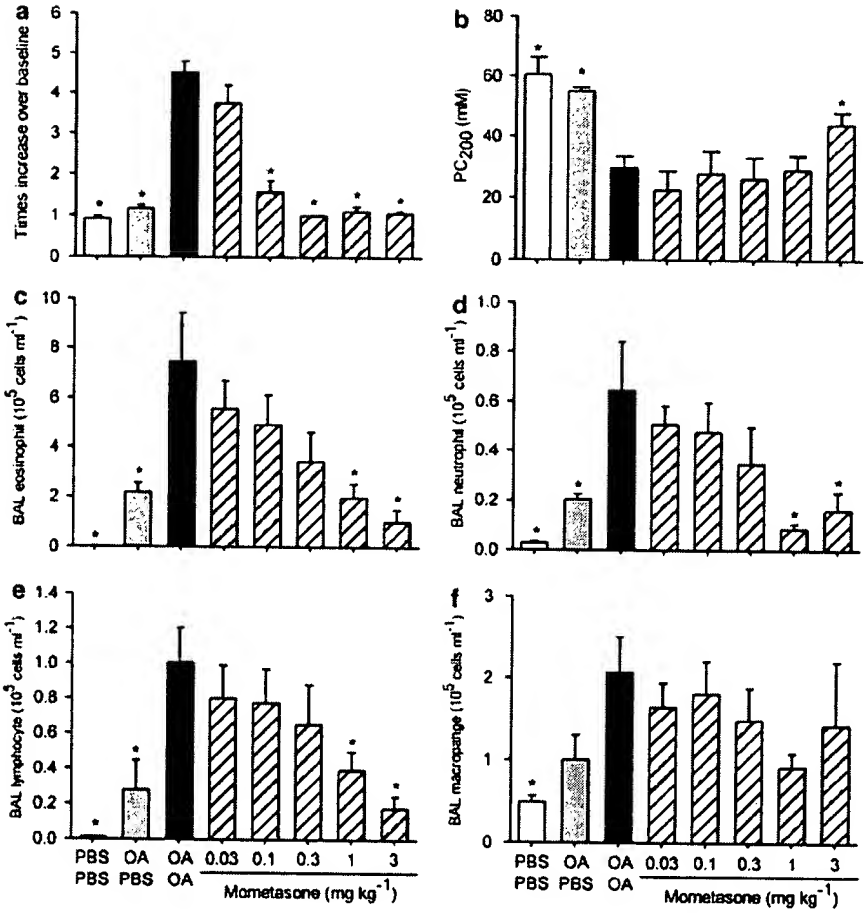

Figure 1 Effect of mometasone, given an hour before the last allergen challenge, on ovalbumin (OA)-induced, increase in Penh (**a**), increased airway sensitivity to aerosolized methacholine (**b**) and influx of bronchoalveolar lavage (BAL) eosinophils (**c**), neutrophils (**d**), lymphocytes (**e**) and macrophages (**f**). Actively sensitized animals were challenged with aerosolized OA or its vehicle PBS on days 21–23 after the first sensitization. On day 26, mice were intranasally treated with mometasone and 1 h later either challenged with an aerosolized solution of OA (OA/OA) or phosphate-buffered saline (PBS; OA/PBS). As a control, a group of sensitized animals was challenged with PBS on days 21–23 and 26 (PBS/PBS) and treated with vehicle. Results are expressed as means ± s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons, $^*P<0.05$ when compared with the OA/OA group.

significantly decreased PC_{200} value in the latter group (Figure 1b). Mometasone inhibited the increased airway sensitivity to aerosolized methacholine at the highest dose tested, 3 mg kg^{-1} (Figure 1b). In the PBS/PBS group, the BAL cells were mainly macrophages with few neutrophils and lymphocytes. In the OA/PBS group, a significant increase in neutrophil, eosinophil and lymphocyte numbers was observed (Figures 1c–e). Eosinophil, neutrophil and lymphocyte numbers were further increased in the OA/OA group and this was dose-dependently inhibited by mometasone, given an hour before the last challenge (Figures 1c–e). When compared with the OA/PBS group, the macrophage numbers were not significantly different in the OA/OA group and mometasone had no effect on this cell type (Figure 1f).

Effect of formoterol

In a first experiment, formoterol (1.5–150 μg kg^{-1}) was given, intranasally, an hour before the last OA challenge. Under these conditions, the drug had no or only a minimal effect on the allergen-induced increase in Penh and BAL inflammatory cell influx. In contrast, a significant decrease in the PC_{200} values was observed at a dose of 150 μg kg^{-1} (Table 1).

In contrast to the pre-allergen challenge treatment regime, when given either 1 or 3 h after the last allergen challenge, formoterol dose-dependently inhibited the allergen-induced increase in Penh measured 4 h after the challenge (Figure 2a). The efficacy of the drug was similar whether it was given 1 or 3 h after the challenge, with a maximal inhibition of 55% (Figure 2a). One day after the last OA challenge, the animals from the OA/OA group were hypersensitive to aerosolized methacholine when compared with the OA/PBS group, and a significant inhibition was only evident for the highest dose of formoterol (150 μg kg^{-1}) in the animals treated 3 h after the challenge (Figure 2b).

When compared with the OA/PBS group, the animals in the OA/OA group had a significant increase in the number of eosinophils, neutrophils and lymphocytes and a significant

Table 1 Effect of formoterol, given intranasally an hour before the allergen challenge, on allergen-induced increase in Penh, airway space cellular infiltration and increased airway sensitivity to aerosolized methacholine

	Allergen-induced increase in Penh (times increase)	*BAL eosinophils (10^5 cells ml^{-1})*	*BAL neutrophils (10^5 cells ml^{-1})*	*BAL macrophages (10^5 cells ml^{-1})*	*BAL lymphocytes (10^5 cells ml^{-1})*	*PC_{200} (mM)*
PBS/PBS	0.94±0.02*	0.01±0.01*	0.01±0.01*	0.58±0.09*	0.01±0.01*	89.2±6.4*
OA/PBS	0.98±0.03*	3.09±0.47*	0.08±0.04*	2.28±0.71*	0.86±0.09*	63.3±9.4*
OA/OA	2.70±0.21	9.57±0.58	0.60±0.16	3.17±0.42	2.01±0.22	42.5±10.1
Formoterol						
1.5 μg kg^{-1}	2.50±0.25	6.90±1.07	1.55±0.14*	2.52±0.25	1.42±0.18	50.1±14.3
5 μg kg^{-1}	3.32±0.56	7.66±1.15	1.62±0.45*	2.21±0.25	1.29±0.18*	44.3±12.9
15 μg kg^{-1}	3.11±0.50	7.32±1.67	0.78±0.15	3.27±0.63	1.24±0.5*	48.4±16.2
50 μg kg^{-1}	2.38±0.41	6.43±0.54*	0.53±0.10	1.54±0.20*	1.11±0.24*	24.5±4.2
150 μg kg^{-1}	3.67±0.30	6.31±0.56*	0.39±0.07	1.83±0.17*	1.34±0.14*	14.2±3.1*

Abbreviations: BAL, bronchoalveolar lavage; OA, ovalbumin; PBS, phosphate-buffered saline; PC_{200}, concentration of methacholine that produced a 200% increase above baseline of the Penh value.
Actively sensitized animals were challenged with aerosolized OA or its vehicle PBS on days 21–23 after the first sensitization. On day 26, mice were either challenged with an aerosolized solution of OA (OA/OA) or PBS (OA/PBS). As a control, a group of sensitized animals was challenged with PBS on days 21–23 and 26 (PBS/PBS). Results are expressed as means±s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons.
*$P<0.05$ when compared with the OA/OA group.

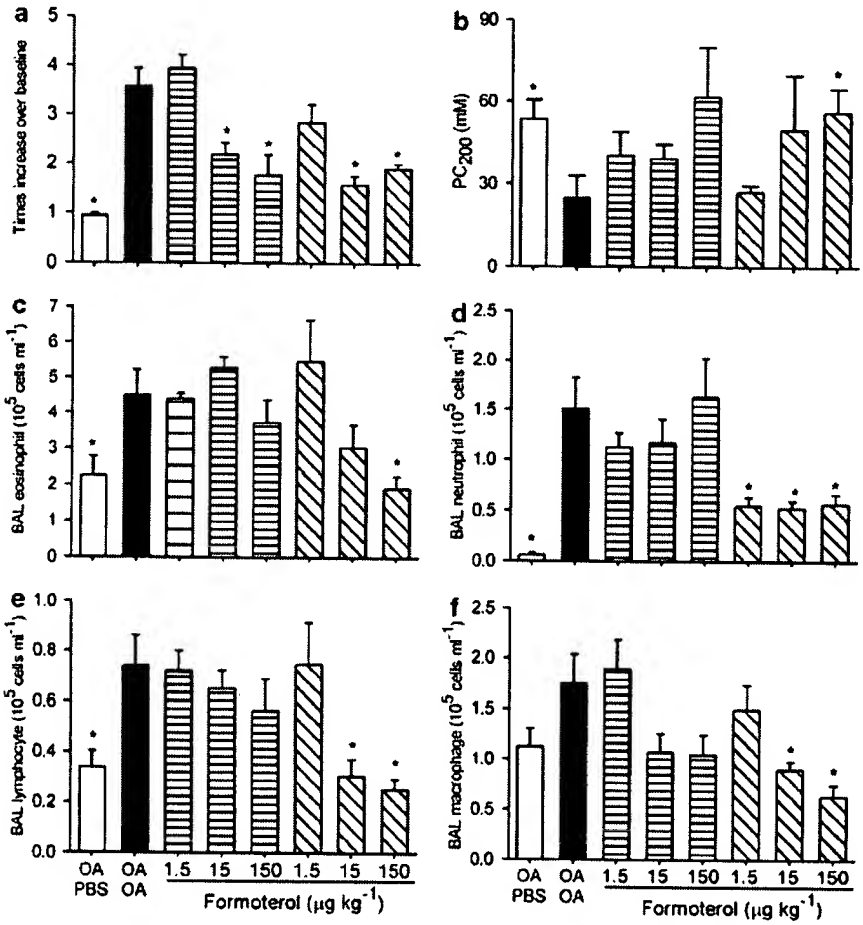

Figure 2 Effect of formoterol, given 1 or 3 h after the last allergen challenge, on ovalbumin (OA)-induced, increase in Penh (**a**), increased airway sensitivity to aerosolized methacholine (**b**) and influx of bronchoalveolar lavage (BAL) eosinophils (**c**), neutrophils (**d**), lymphocytes (**e**) and macrophages (**f**). Actively sensitized animals were challenged with aerosolized OA or its vehicle phosphate-buffered saline (PBS) on days 21–23 after the first sensitization. On day 26, mice were either challenged with an aerosolized solution of OA (OA/OA) or PBS (OA/PBS) and were intranasally treated with formoterol 1 h (horizontally hatched columns) or 3 h (diagonally hatched columns) later. Results are expressed as means±s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons, *$P<0.05$ when compared with the OA/OA group.

inhibition was observed only when formoterol was given 3 h after the challenge (Figures 2c–e). Although macrophage numbers were not significantly increased by the OA challenge, formoterol, when given 3 h after the challenge but not if given 1 h after, did significantly inhibit the number of this cell type (Figure 2f).

Effect of mometasone given an hour after the allergen challenge

As formoterol was shown to be inactive when given before the last OA challenge, and since both compounds had to be given at the same time in the combination experiment, it was necessary to establish the dose–response data for mometasone when given after the allergen challenge. Mometasone, given an hour after the last allergen challenge, dose-dependently inhibited the allergen-induced increase in Penh with about a 10-fold loss of potency when compared with the pre-challenge treatment schedule (Figure 3a). The increased airway sensitivity to aerosolized methacholine (Figure 3b) and the inflammatory cell influx (Figures 3c–f) was dose-dependently inhibited with a similar potency, when compared with the pre-challenge treatment schedule.

Effect of the combination of mometasone and formoterol given an hour after the last allergen challenge

To study a possible synergistic effect of mometasone and formoterol in this model, animals were either treated with three doses of each of the drugs alone (formoterol: 1, 5 and 15 $\mu g\,kg^{-1}$; mometasone: 10, 100 and 300 $\mu g\,kg^{-1}$) or with four different combinations (formoterol/mometasone in $\mu g\,kg^{-1}$: 1/10, 5/10, 1/100 and 5/100). As formoterol was shown to be inactive when given before the last OA challenge, and since both compounds had to be given at the same time, all animals were treated an hour after the last allergen challenge.

Both formoterol and mometasone dose-dependently inhibited the allergen-induced increase in Penh. A significant, but incomplete inhibition was observed at doses of 15 and 300 $\mu g\,kg^{-1}$ for formoterol and mometasone, respectively. All

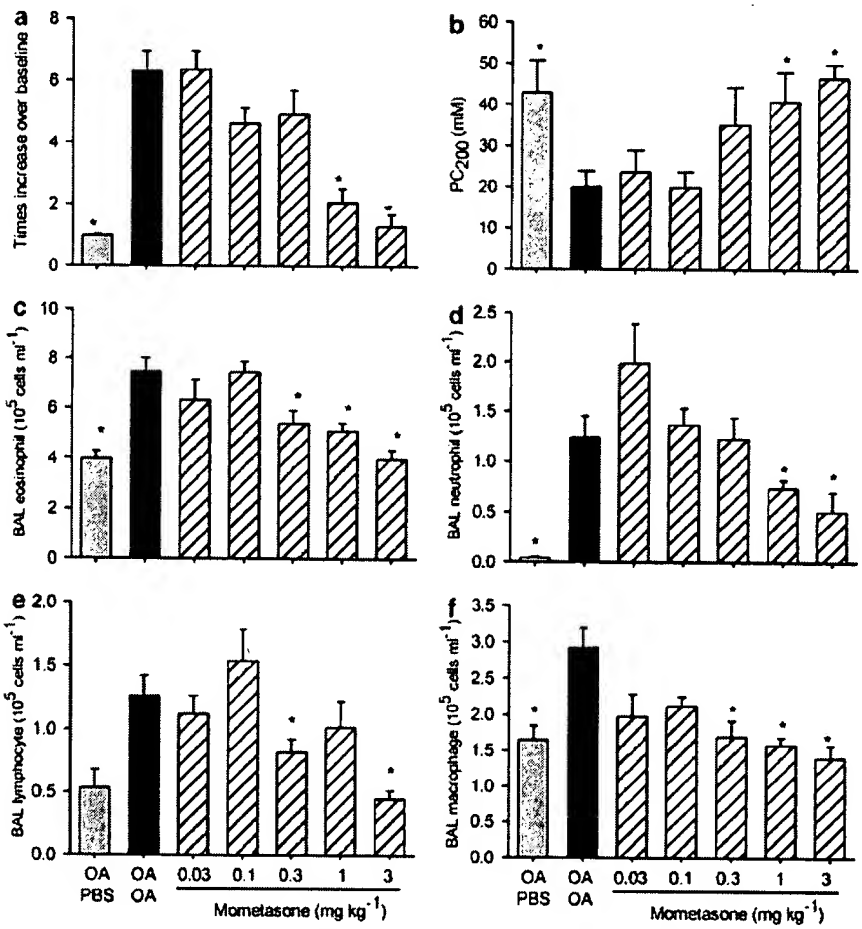

Figure 3 Effect of mometasone, given 1 h after the last allergen challenge, on ovalbumin (OA)-induced, increase in Penh (**a**), increased airway sensitivity to aerosolized methacholine (**b**) and influx of bronchoalveolar lavage (BAL) eosinophils (**c**), neutrophils (**d**), lymphocytes (**e**) and macrophages (**f**). Actively sensitized animals were challenged with aerosolized OA or its vehicle phosphate-buffered saline (PBS) on days 21–23 after the first sensitization. On day 26, mice were either challenged with an aerosolized solution of OA (OA/OA) or PBS (OA/PBS) and were intranasally treated with mometasone or its vehicle 1 h later. Results are expressed as means ± s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons, $^*P<0.05$ when compared with the OA/OA group.

combinations, apart from 1 $\mu g\,kg^{-1}$ formoterol together with 10 $\mu g\,kg^{-1}$ mometasone, significantly inhibited the allergen-induced increase in Penh (Figure 4). Berenbaum's analysis demonstrated a synergistic effect for all four combinations tested when compared with the single entities with a coefficient of 0.23, 0.45, 0.24 and 0.32 for the formoterol/mometasone combinations of 1/10, 5/10, 1/100 and 5/100 $\mu g\,kg^{-1}$, respectively. Formoterol, up to the highest dose tested, 15 $\mu g\,kg^{-1}$, had no effect on the OA-induced increased airway sensitivity to aerosolized methacholine. In contrast, mometasone did fully inhibit this response at a dose of 300 $\mu g\,kg^{-1}$. None of the combinations tested had a significant effect on the increased airway sensitivity to aerosolized methacholine (Table 2). All the inflammatory cell types were increased after the OA challenge, but only eosinophils were inhibited by the highest dose of mometasone (300 $\mu g\,kg^{-1}$) and neutrophils by the combination of formoterol 5 $\mu g\,kg^{-1}$ together with mometasone 100 $\mu g\,kg^{-1}$ (Table 2). Since neither formoterol nor mometasone, at the doses used, had a significant effect on the increased airway sensitivity to aerosolized methacholine or the inflammatory cell influx, Berenbaum's analysis could not be applied.

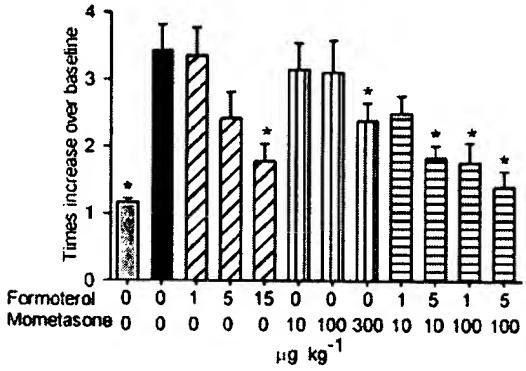

Figure 4 Effect of formoterol, mometasone or their combination, given 1 h after the last allergen challenge, on ovalbumin (OA)-induced, increase in Penh. Actively sensitized animals were challenged with aerosolized OA or its vehicle phosphate-buffered saline (PBS) on days 21–23 after the first sensitization. On day 26, mice were either challenged with an aerosolized solution of OA (OA/OA) or PBS (OA/PBS), and were intranasally treated with formoterol, mometasone or their combinations mometasone or its vehicle 1 h later. Results are expressed as means±s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons, *$P<0.05$ when compared with the OA/OA group.

Discussion

In this study, we have shown that formoterol and mometasone, two clinically used drugs, act synergistically to inhibit the allergen-induced increase in Penh observed in allergen-sensitized and challenged mice.

Because we wanted to measure all parameters (lung function and airway inflammation) within the same animal, the lung function measurements were done using unrestrained barometric whole body plethysmography and expressed as Penh value. The use of Penh to assess lung function is controversial (Adler *et al.*, 2004; Schwarze *et al.*, 2005) and we recognized that Penh is not a substitute for established parameters of lung mechanics. However, a good correlation between airway resistance and Penh has been demonstrated in BALB/c mice, the strain used in our study

Table 2 Effects of formoterol, mometasone and their combinations, given an hour after the allergen challenge, on increased airway sensitivity to aerosolized methacholine and airway space cellular infiltration

	PC_{200} (mM)	Eosinophils (10^5 cells ml^{-1})	Neutrophils (10^3 cells ml^{-1})	Lymphocytes (10^5 cells ml^{-1})	Macrophages (10^5 cells ml^{-1})
OA/PBS	39.4±7.4*	4.7±0.7*	5.5±2.3*	0.7±0.2*	2.0±0.3*
OA/OA	22.1±4.6	10.0±0.8	29.7±7.5	1.6±0.2	4.9±0.5
Formoterol ($\mu g\,kg^{-1}$)					
1	23.6±4.9	11.2±1.4	18.1±4.4	1.2±0.2	3.5±0.4
5	23.8±2.2	10.3±1.9	13.7±3.6	1.9±0.3	3.0±0.6
15	27.3±3.1	12.3±1.5	46.4±14.9	2.1±0.4	4.4±0.9
Mometasone ($\mu g\,kg^{-1}$)					
10	30.1±7.1	9.3±0.8	46.1±7.2	1.7±0.2	5.1±0.5
100	33.7±4.1	9.9±1.8	42.2±13.1	1.6±0.5	4.1±1.0
300	41.2±6.7*	5.7±0.8*	35.5±6.3	1.2±0.2	3.6±0.8
Formoterol/mometasone ($\mu g\,kg^{-1}$)					
1/10	33.1±3.3	7.2±1.2	19.9±4.3	1.2±0.3	3.2±0.6
5/10	29.6±3.2	8.8±1.0	16.6±5.0	1.2±0.3	3.6±0.5
1/100	33.1±4.0	7.9±1.8	15.0±5.0	1.8±0.6	3.4±0.6
5/100	33.0±7.4	9.7±1.5	6.5±3.1*	1.5±0.4	3.1±0.8

Abbreviations: OA, ovalbumin; PBS, phosphate-buffered saline; PC_{200}, concentration of methacholine that produced a 200% increase above baseline of the Penh value.

Actively sensitized animals were challenged with aerosolized ovalbumin or its vehicle PBS on days 21–23 after the first sensitization. On day 26, mice were either challenged with an aerosolized solution of ovalbumin (OA/OA) or PBS (OA/PBS). Animals were intranasally treated with formoterol, mometasone or their combination. Results are expressed as means±s.e.mean from one experiment with 7–8 animals per group. Statistical comparisons were performed using a Mann–Whitney test with Bonferroni correction for multiple comparisons.

*$P<0.05$ when compared with the OA/OA group.

(Adler *et al.*, 2004). Moreover, it was previously demonstrated that the airway response to allergen challenge in the present model was equivalent whether it was measured using Penh in conscious mice or airway resistance in anaesthetized animals (Cieslewicz *et al.*, 1999).

There is growing evidence *in vitro* that β_2-adrenoceptor agonists and corticosteroids have complementary and synergistic effects. In both primary lung fibroblasts (Eickelberg *et al.*, 1999) and primary bronchial smooth muscle cells (Roth *et al.*, 2002) from humans, β_2-adrenoceptor agonists have been shown to induce ligand-independent activation of the corticosteroid receptor. Importantly, the combination of low doses of β_2-adrenoceptor agonists and corticosteroids resulted in a synchronized activation of the corticosteroid receptor suggesting a synergistic effect of the two drugs in inhibiting cellular proliferation (Roth *et al.*, 2002). This synchronized activation of the corticosteroid receptor by β_2-adrenoceptor agonists has recently been confirmed in healthy volunteers (controls) and patients with mild asthma, where combination therapy with low dose of inhaled corticosteroid and inhaled β_2-adrenoceptor agonist augmented the activation of the corticosteroid receptor when compared with the single entities (Usmani *et al.*, 2005). On the other hand, corticosteroids also have positive effects on the β_2-adrenoceptor. As such, β_2-adrenoceptor transcription is increased by corticosteroid treatment in human lung tissue *in vitro* (Mak *et al.*, 1995) or in human nasal mucosa *in vivo* (Baraniuk *et al.*, 1997). A positive interaction between corticosteroids and β_2-adrenoceptor agonists has also been demonstrated on the inhibition of the release of cytokines from human airway smooth muscle (Pang and Knox, 2000) and airway epithelial cells (Korn *et al.*, 2001). All these studies showed positive interactions between steroids and the β_2-adrenoceptor, but none of them clearly demonstrated a synergistic effect between these two classes of compound.

Although our data clearly show a synergistic effect of formoterol and mometasone *in vivo*, the precise cell type and/or inflammatory events affected by the two drugs is not clear. Both corticosteroids (Nocker *et al.*, 1999) and β_2-adrenoceptor agonists (Greiff *et al.*, 1998; Proud *et al.*, 1998) are known to inhibit plasma leakage, and, therefore, one can hypothesize that in our model, the increase in Penh is driven by an increased vascular leakage and that the synergistic effect seen with formoterol and mometasone is linked to their anti-plasma leakage properties. We did not assess plasma leakage in the present study, but a previous study has shown that following allergen challenge, mice only develop an early plasma exudation (within 15 min post challenge) and that no late exudation phase can be observed, even following repeated allergen challenges (Erjefalt *et al.*, 1998). Since we measured the increase in Penh at 4 h after the allergen challenge, it is unlikely to be linked to plasma exudation.

In our model and in line with its clinical profile, formoterol, given after the allergen challenge, has only a marginal inhibitory effect on the eosinophil influx and inhibits the allergen-induced airway increased airway sensitivity to aerosolized methacholine. This is the reason why the synergistic effect of the mometasone/formoterol combination could not be assessed on these two parameters. Indeed, to study synergy using the method described by Berenbaum (1977), both components should be able to inhibit the parameter studied when given on their own. Nevertheless, our data suggest a positive interaction between the two drugs on the allergen-induced airway neutrophilia, since both drugs were inactive when given on their own and a significant inhibition was observed with a combination of $5\,\mu g\,kg^{-1}$ formoterol and $100\,\mu g\,kg^{-1}$ mometasone. Knowing that steroids are not very effective in promoting the resolution of neutrophilic inflammation, this observation could have significant clinical implications for patients with severe asthma where neutrophil is thought to be the dominant inflammatory cell (Kamath *et al.*, 2005).

It is noteworthy that when given as a single entity an hour before the allergen challenge, formoterol had a deleterious effect on the airway reactivity to aerosolized methacholine. A possible explanation for this phenomenon could be related to the bronchodilating property of this class of compound that would facilitate the penetration of the antigen within the small airways, thereby, enhancing the airway reactivity to aerosolized methacholine. In support of this interpretation is the fact that when given either 1 or 3 h after the allergen challenge such a deleterious effect is not seen with formoterol.

In summary, our results demonstrate that coadministration of formoterol and mometasone, in a murine model of allergen-induced lung inflammation, acts synergistically when compared to the single administration of each drug. This observation supports the concept that when given as a fixed-dose combination to asthmatic patients, these drugs act synergistically.

Conflict of interest

All authors are permanent employees of Novartis Pharma. Novartis Pharma, together with Schering-Plough, is developing a fixed-dose combination inhaler containing formoterol and mometasone.

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EXHIBIT 6

US006068832A

United States Patent [19]

Berry et al.

[11] Patent Number: 6,068,832

[45] Date of Patent: May 30, 2000

[54] **CHLOROFLUOROCARBON-FREE MOMETASONE FUROATE AEROSOL FORMULATIONS**

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[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: **08/920,611**

[22] Filed: **Aug. 27, 1997**

Related U.S. Application Data

[60] Provisional application No. 60/025,807, Aug. 29, 1996.

[51] **Int. Cl.**[7] **A61K 9/12**

[52] **U.S. Cl.** **424/45**; 424/46

[58] **Field of Search** 424/45, 46

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Primary Examiner—Raj Bawa
Attorney, Agent, or Firm—Robert A. Franks

[57] **ABSTRACT**

The invention relates to suspension aerosol formulations which exhibit stable particle sizes, containing mometasone furoate, about 1 to about 10 weight percent ethanol and 1,1,1,2,3,3,3-Heptafluoropropane as the propellant. A surfactant, such as oleic acid, can also be included. These formulations are suitable for use in metered dose inhalers.

18 Claims, No Drawings

CHLOROFLUOROCARBON-FREE MOMETASONE FUROATE AEROSOL FORMULATIONS

This application claims benefit of provisional application Ser. No. 60/025,807 filed Aug. 29, 1996.

INTRODUCTION TO THE INVENTION

The present invention pertains to aerosol formulations of drugs, such as those formulations suitable for use in pressurized aerosol metered dose inhalers. More specifically, the invention relates to aerosol formulations of the drug mometasone furoate with the propellant 1,1,1,2,3,3,3-Heptafluoropropane (HFC-227).

Aerosolized drugs have been used for many years to treat disorders of the respiratory system, and as a convenient means for the systemic introduction of various pharmaceutical agents into the body. The typical aerosol formulation in a metered dose inhaler for treating disorders such as asthma or rhinitis is a suspension of one or more drug substances in a fully halogenated (with chlorine and fluorine) lower alkyl compound propellant, further containing small amounts of surfactants and/or excipients which are usually soluble in the propellant.

Pharmaceutical agents administered by means of metered dose inhalers are usually bronchodilators or corticosteroids. The steroidal drugs which are currently available in this form for inhalation therapeutic uses in the United States include beclomethasone dipropionate (both for nasal and lower airway administration), budesonide (nasal and airway administration), dexamethasone sodium phosphate (nasal and airway administration), flunisolide (nasally administered), and triamcinolone acetonide (nasal and airway administration). Fluticasone propionate has also recently been approved for sale as a lower airway drug. Typical formulations contain chlorofluorocarbon propellants, the drug substance and ethanol, which is soluble in the propellant, and sometimes also contain a surfactant such as oleic acid for maintaining a stable suspension, lubrication of the metering valve and other functions.

However, certain of the steroids have significant solubility in ethanol. When there is insufficient ethanol present for maintaining a solution of these drugs in an aerosol canister, the normal temperature fluctuations encountered during storage and use can cause repeated solubility increases and decreases of a saturated solution. Each time the drug substance becomes less soluble, such as in a period of ambient temperature decrease, it tends to crystallize and, due to the typical slow rate of temperature change, grows into crystals much larger than those which can be properly dispensed—particularly when the drug is intended for delivery to the bronchia or lungs. In general, drug particle sizes from about 1 to about 5 micrometers are preferred for administration to the lower airway, with particles smaller than about 0.5 micrometers frequently being exhaled without complete deposition on tissues, while particles larger than about 10 micrometers can exhibit considerable deposition in the mouth and/or pharynx and therefore not reach the lower airway. Very large particles cannot pass through a metering valve and will not be reliably dispensed.

In the case of beclomethasone dipropionate, itself quite soluble in ethanol, an addition compound (sometimes called a "solvate" or "clathrate") can be formed from the compound and the chlorofluorocarbons or a fluorohydrocarbon; when this clathrate is formulated with a propellant, no particle size growth is noted.

With the implication of fully halogenated chlorofluorocarbon propellants in the environmentally harmful destruction of ozone in the upper atmosphere, the availability of these propellants has become quite restricted. This has encouraged development work toward formulations containing propellants having reduced upper atmospheric reactivity, such work particularly centering about the propellants 1,1,1,2-Tetrafluoroethane (HFC-134a) and HFC-227, these compounds having approximately the same physical properties as those of the older chlorofluorocarbons used for medicinal aerosols. Recent studies have imputed to HFC-134a an undesirable potential for surface water acidification, as it appears to form the environmentally very stable trifluoroacteic acid in the atmosphere.

It has been proposed in European Patent 0 553 298 B1 to formulate an aerosol with HFC-134a by simply including sufficient ethanol to maintain beclomethasone dipropionate in solution over at least the expected ambient temperature range. However, the presence of any ethanol is discouraged in many countries, due to the prevalence of alcoholism and the ease with which ethanol is systemically absorbed from lower airway tissues. Any products intended for use by children generally should have as low an ethanol content as possible.

International Patent Application WO 93/11745 discloses particle size-stable suspension aerosol formulations containing drug substances, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, and a polar cosolvent such as an alcohol. No surfactants are said to be required.

International Patent Application WO 94/03153 reports that solvates of beclomethasone and HFC-134a can be used to produce stable suspensions in a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, in the substantial absence of solvating species such as alcohol.

The drug mometasone furoate would have advantages over the presently available corticosteroids for treating airway disorders. As reported in International Patent Application WO 95/20393, the drug has a very rapid onset of action and generally does not appear in detectable concentrations in the blood, following nasal or airway administration.

Unfortunately, this drug has some solubility in ethanol and exhibits particle size increases during storage of suspension aerosol formulations prepared using large amounts of ethanol.

International Patent Applications WO 92/22287 and WO 92/22288 disclose aerosol formulations of mometasone furoate in the propellants HFC-134a and HFC-227, but do not address the problem of adverse particle size increases.

SUMMARY OF THE INVENTION

In accordance with the invention, there is provided a particle size-stable pressurized aerosol suspension formulation of mometasone furoate, comprising the propellant HFC-227, about 1 to about 10 weight percent ethanol and mometasone furoate in concentrations at least about 1 percent of the ethanol concentration. The formulation can also contain a surfactant.

It has been discovered that the formulation of the invention does not exhibit significant particle size changes in the suspended drug. In addition, the densities of the solid and liquid phases are similar, giving a suspension which has a reduced tendency for particle settling; this results in a greatly facilitated re-dispersion into a uniform suspension, after the formulation has remained in an undisturbed condition for prolonged periods.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides pressurized aerosol formulations of the corticosteroid drug mometasone furoate, particularly formulations suitable for use in metered dose inhalers.

Mometasone furoate is also known by the chemical name 9α,21-Dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), has the empirical formula $C_{27}H_{30}Cl_2O_6$ and has a molecular weight of 521.44. The drug is currently marketed in cream, ointment and lotion formulations, for the treatment of various dermatological conditions.

In formulations of the present invention which are suitable for treating lower respiratory system disorders such as asthma, at least a substantial portion of the drug is present as suspended particles having respirable sizes, e.g., about 0.5 to about 10 micrometers in their largest dimension. In inventive formulations which are suitable for treating upper respiratory system disorders such as rhinitis, somewhat larger drug particles may be permissible, but the foregoing size range remains preferred.

As with other drugs which have appreciable solubility in ethanol, there is a tendency for mometasone furoate to exhibit crystal growth in ethanol-containing formulations. However, the inventors have discovered formulation parameters which do not promote drug particle size growth. These parameters also provide the advantage of minimizing the required ethanol concentrations, to reduce the potential for unpleasant taste sensations and render the compositions more suitable for use by children and others with low alcohol tolerance.

It has been discovered that a certain minimum level of ethanol is needed to provide consistent and predictable delivery of the drug from a metered dose dispenser. This minimum level is about 1 weight percent of the total formulation, which results in a marginally acceptable drug delivery. Increased amounts of ethanol generally improve drug delivery characteristics.

However, for reasons previously discussed, and to prevent drug crystal growth in the formulation, it is necessary to limit the concentration of ethanol. Experimental data indicate that the ratio of the weight of mometasone furoate to the weight of ethanol is important in preventing particle size increases; in general, when the drug is present at 0.6 percent of the concentration of ethanol, immediate and severe adverse changes in crystal morphology and size are observed. This effect is not seen when the mometasone furoate is present at 1.3 percent of the ethanol concentration, leading to a conclusion that the drug must be present in concentrations at least about 1 percent of the ethanol concentration.

Limitations in the available metering valve delivery volumes (e.g., 25 to 100 microliters per actuation) and the amounts of drug substance required in a dose for treating a particular condition (generally about 10 to about 500 micrograms per valve actuation) will dictate the points within the foregoing ethanol parameters for a given formulation. Determination of such amounts is well within the skill of workers in this art.

A surfactant is frequently included in aerosol formulations, for purposes such as assisting with maintaining a stable suspension of the drug and lubricating the metering valve. The formulation of the present invention does not require a surfactant for maintenance of ready dispersability (such as by moderate agitation immediately prior to use), as the drug forms loose flocculates in the propellant and does not exhibit a tendency to settle or compact. Upon undisturbed storage, the drug particles merely remain in their flocculated state.

However, surfactants can be incorporated, in small amounts as are customary in other aerosol suspensions, to ensure proper metering valve function. The commonly used oleic acid is suitable, at levels which will deliver up to about 50 micrograms of oleic acid per actuation of the valve. Of course, it is always desired to minimize the amounts of chemical substances in a medication dose, so the lowest concentrations which yield the desired effects are to be used. Other useful surfactants include, without limitation thereto, sorbitan trioleate, cetyl pyridinium chloride, soya lecithin, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (10) stearyl ether, polyoxyethylene (2) oleyl ether, polyoxyethylene-polyoxypropylene-ethylenediamine block copolymers, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene-polyoxypropylene block copolymers, castor oil ethoxylate, and mixtures of any of the surfactants. It is generally preferred that the surfactant is soluble, at levels employed, in the alcohol-propellant solution. For any desired surfactant, simple experiments to measure drug delivery reproducibility can be employed to identify the optimum amount of surfactant for any given formulation and delivery system.

Formulations of the invention are made according to procedures customary in the art for other aerosol compositions. Typically, all components except the propellant are mixed and introduced into aerosol containers. The containers can then be chilled to temperatures below the boiling point of the propellant, and the required amount of the chilled propellant added before the metering valve is crimped onto the container. Alternatively, the containers can be fitted with a metering valve before being filled with propellant, and the required quantity of propellant will be introduced through the valve.

Certain aspects of the invention are further described in the following examples. In the examples, "percent" indicates weight percentage unless the context clearly indicates otherwise.

EXAMPLE 1

Following are examples of useful aerosol suspension formulations, according to the present invention. Ingredient amounts, in percent of mometasone furoate ("MF"), oleic acid ("Oleic"), ethanol ("EtOH") and HFC-227 ("Propellant"), are given.

Formulation	MF	Oleic	EtOH	Propellant
A	0.112	0.001	2.497	97.389
B	0.028	0	1.750	98.222
C	0.112	0.011	2.497	97.379
D	0.448	0.011	2.489	97.052
E	0.112	0	2.497	97.390
F	0.448	0.011	4.977	94.564
G	0.224	0.011	2.494	97.270
H	0.028	0.001	2.499	97.471
I	0.028	0.011	2.499	97.462

EXAMPLE 2

Experiments are performed to determine the effects on aerosol drug delivery characteristics from variable, low concentrations of ethanol. In these experiments, micronized mometasone furoate is incorporated into a "concentrate" suspension with the ethanol and, optionally, oleic acid. A required amount of the well-mixed concentrate for delivery of 120 doses is weighed into metal aerosol containers, a metering valve delivering 63 microliters per actuation (a volume containing 100 micrograms of mometasone furoate)

is crimped onto the container and liquid HFC-227 propellant is weighed into the container through the valve. The concentration of mometasone furoate in the final formulation is 0.112%.

To test drug delivery from the containers, the weight of drug substance delivered by two actuations of the metering valve is measured, and divided by two to calculate the amount delivered in a single actuation. After a fixed number of "priming" actuations, this is done for the first two doses delivered from the container, two doses at the midpoint of doses to be delivered and two doses at the end of the intended capacity of the container. Tabulated below are average amounts recovered from multiple containers of each formulation, the formulation information identifying the amount of oleic acid delivered with each valve actuation.

1% Ethanol, 2.5 μg Oleic Acid (6 containers)	
Beginning	75.2 μg
Midpoint	83.4 μg
End	92.6 μg
1.75% Ethanol, 10 μg Oleic Acid (6 containers)	
Beginning	94.3 μg
Midpoint	96.4 μg
End	110 μg
2.5% Ethanol, 10 μg Oleic Acid (10 containers)	
Beginning	104 μg
Midpoint	102 μg
End	106 μg
2.5% Ethanol, no Oleic Acid (10 containers)	
Beginning	93.3 μg
Midpoint	98.8 μg
End	99.0 μg

The drug delivery from those containers having 1 percent ethanol could be marginally acceptable for a commercial product, while deliveries from all of the containers with higher alcohol level formulations would be acceptable. The general drug delivery standards for inhalation products intended to treat asthma are established by governmental agencies, such as the United States Food and Drug Administration.

EXAMPLE 3

Experiments are conducted to determine the effects on drug particle size stability of variable ratios of drug to ethanol weights in aerosol formulations.

Formulations are prepared in glass containers, fitted with aerosol valves, from the following components, where amounts are in percent:

Formulation A	
HFC-227	94.969
Ethanol	4.985
Mometasone Furoate	0.034
Oleic Acid	0.012
Mometasone Furoate/Ethanol = 0.00674	
Formulation B	
HFC-227	97.457
Ethanol	2.499
Mometasone Furoate	0.032
Oleic Acid	0.011

-continued

Mometasone Furoate/Ethanol = 0.0130	
Formulation C	
HFC-227	97.366
Ethanol	2.497
Mometasone Furoate	0.127
Oleic Acid	0.011
Mometasone Furoate/Ethanol = 0.0508	
Formulation D	
HFC-227	97.188
Ethanol	2.492
Mometasone Furoate	0.308
Oleic Acid	0.011
Mometasone Furoate/Ethanol = 0.124	

Each formulation is examined for evidence of crystal growth after preparation, by visually inspecting the container contents and by spraying a dose of the formulation onto a glass microscope slide, allowing the propellant to evaporate and visually inspecting particles on the slide with polarized light at 100X magnification. Formulation A shows extensive crystal morphology change, into elongated needle-like shapes, of which many have a maximum dimension appearing to be greater than about 30 μm; the changes are visually apparent in the container without any magnification. Particles in each of the other formulations appear similar to those of the original micronized mometasone furoate, both in particle form and in size. Formulation A will not be suitable for the inhalation delivery of mometasone furoate.

The containers with Formulations B, C and D are subjected to a freeze/thaw temperature program, as follows: −20° C. for 3 days, then room temperature for one day, then 50° C. for 2 days, then −20° C. for 4 days, then 50° C. for 3 days, then −20° C. for 3 days, then 50° C. for 3 days, and finally room temperature for 1 day. Upon repeating the microscopic examination, no temperature excursion-induced changes in particle form or size are observed in any of these formulations.

The foregoing descriptions of various embodiments of the invention are representative of various aspects of the invention, and are not intended to be exhaustive or limiting to the precise forms disclosed. Many modifications and variations undoubtedly will occur to those having skill in the art. It is intended that the scope of the invention shall be fully defined solely by the appended claims.

What is claimed is:

1. An aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane, about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

2. The aerosol suspension formulation of claim 1, comprising about 1 to about 5 weight percent ethanol.

3. The aerosol suspension formulation of claim 1, comprising about 2 to about 5 weight percent ethanol.

4. The aerosol suspension formulation of claim 1, which contains a surfactant.

5. The aerosol suspension formulation of claim 4, wherein the surfactant comprises oleic acid.

6. The aerosol suspension formulation of claim 1, which is contained in a metered dose container.

7. The aerosol suspension formulation of claim 1, which is contained in apparatus delivering a measured amount of about 10 to about 500 micrograms of mometasone furoate from a single actuating operation.

8. A method for treating allergic reactions in the respiratory tract, comprising administering by inhalation an aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane, about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

9. The method of claim 8, wherein the suspension comprises about 1 to about 5 weight percent ethanol.

10. The method of claim 8, wherein the suspension comprises about 2 to about 5 weight percent ethanol.

11. The method of claim 8, wherein the suspension contains a surfactant.

12. The method of claim 11, wherein the surfactant comprises oleic acid.

13. The method of claim 8, wherein the suspension is contained in a metered dose container.

14. The method of claim 8, wherein the suspension is contained in apparatus delivering a measured amount of about 10 to about 500 micrograms of mometasone furoate from a single actuating operation.

15. A metered dose inhaler which contains an aerosol suspension formulation comprising 1,1,1,2,3,3,3-Heptafluoropropane, about 1 to about 10 weight percent ethanol and micronized mometasone furoate in concentrations at least about 1 percent of the ethanol concentration, the formulation optionally also containing a surfactant.

16. The metered dose inhaler of claim 15, wherein about 10 to about 500 micrograms of mometasone furoate are delivered from a single actuating operation.

17. The metered dose inhaler of claim 15, which is adapted for nasal delivery of mometasone furoate.

18. The metered dose inhaler of claim 15, which is adapted for lower airway delivery of mometasone furoate.

* * * * *

EXHIBIT 7

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DATE PRINTED
08/15/2010

ROBERT A. FRANKS
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT, K-6-1, 1990
2000 GALLOPING HILL ROAD

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,068,832	**$890.00**	**$0.00**	**09/26/03**	**08/920,611**	**05/30/00**	**08/27/97**	**04**	**NO**	**PD09586Q**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,068,832	**$2,300.00**	**$0.00**	**09/14/07**	**08/920,611**	**05/30/00**	**08/27/97**	**08**	**NO**	**PD09586Q**

EXHIBIT 8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DULERA safely and effectively. See full prescribing information for DULERA.

DULERA® 100 mcg/5 mcg (mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg) Inhalation Aerosol

DULERA® 200 mcg/5 mcg (mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg) Inhalation Aerosol

FOR ORAL INHALATION

Initial U.S. Approval: 2010

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (1.1, 5.1)**

----------INDICATIONS AND USAGE----------

DULERA is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Treatment of asthma in patients 12 years of age and older. (1.1)

Important limitations:

- Not indicated for the relief of acute bronchospasm. (1.1)

----------DOSAGE AND ADMINISTRATION----------

For oral inhalation only.

Treatment of asthma in patients ≥12 years: 2 inhalations twice daily of DULERA 100 mcg/5 mcg or 200 mcg/5 mcg. Starting dosage is based on prior asthma therapy. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Inhalation aerosol containing a combination of mometasone furoate (100 or 200 mcg) and formoterol fumarate dihydrate (5 mcg) per actuation. (3)

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4.1)
- Hypersensitivity to any of the ingredients of DULERA. (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.5)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to DULERA. (5.6)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue DULERA slowly. (5.7)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with DULERA. (5.8)
- Paradoxical bronchospasm: Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
- Patients with cardiovascular disorders: Use with caution because of beta-adrenergic stimulation. (5.11)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.12)
- Effects on growth: Monitor growth of pediatric patients. (5.13)
- Glaucoma and cataracts: Monitor patients with change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts closely. (5.14)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Hypokalemia and hyperglycemia: Be alert to hypokalemia and hyperglycemia. (5.16)

----------ADVERSE REACTIONS----------

Most common adverse reactions (reported in ≥3% of patients) included:

- Nasopharyngitis, sinusitis and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation, a subsidiary of Merck & Co., Inc., at 1-800-526-4099 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects. (7.1)
- Adrenergic agents: Use with caution. Additional adrenergic drugs may potentiate sympathetic effects. (7.2)
- Xanthine derivatives and diuretics: Use with caution. May potentiate ECG changes and/or hypokalemia. (7.3, 7.4)
- MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval: Use with extreme caution. May potentiate effect on the cardiovascular system. (7.5)
- Beta-blockers: Use with caution and only when medically necessary. May decrease effectiveness and produce severe bronchospasm. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. ***[See Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

DULERA is indicated for the treatment of asthma in patients 12 years of age and older.

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1)]*. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitation of Use

- DULERA is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 General

DULERA should be administered only by the orally inhaled route (see Instructions for Using DULERA in the Medication Guide). After each dose, the patient should be advised to rinse his/her mouth with water without swallowing.

DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

The DULERA canister should only be used with the DULERA actuator. The DULERA actuator should not be used with any other inhalation drug product. Actuators from other products should not be used with the DULERA canister.

2.2 Dosing

DULERA should be administered as two inhalations twice daily every day (morning and evening) by the orally inhaled route. Shake well prior to each inhalation.

The recommended starting dosages for DULERA treatment are based on prior asthma therapy.

Table 1: Recommended Dosages for DULERA

Previous Therapy	Recommended Dose	Maximum Recommended Daily Dose
Inhaled medium dose corticosteroids	DULERA 100 mcg/5 mcg, 2 inhalations twice daily	400 mcg/20 mcg
Inhaled high dose corticosteroids	DULERA 200 mcg/5 mcg, 2 inhalations twice daily	800 mcg/20 mcg

The maximum daily recommended dose is two inhalations of DULERA 200 mcg/5 mcg twice daily. Do not use more than two inhalations twice daily of the prescribed strength of DULERA as some patients are more likely to experience adverse effects with higher doses of formoterol. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be taken for immediate relief.

If a previously effective dosage regimen of DULERA fails to provide adequate control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic options, e.g., replacing the current strength of DULERA with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

The maximum benefit may not be achieved for 1 week or longer after beginning treatment. Individual patients may experience a variable time to onset and degree of symptom relief. For patients ≥12 years of age who do not respond adequately after 2 weeks of therapy, higher strength may provide additional asthma control.

3 DOSAGE FORMS AND STRENGTHS

DULERA is a pressurized metered dose inhaler that is available in 2 strengths.

DULERA 100 mcg/5 mcg delivers 100 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

DULERA 200 mcg/5 mcg delivers 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

DULERA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

4.2 Hypersensitivity

DULERA is contraindicated in patients with known hypersensitivity to mometasone furoate, formoterol fumarate, or any of the ingredients in DULERA *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe DULERA for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABAs, including formoterol, one of the active ingredients in DULERA. No study adequate to determine whether the rate of asthma-related death is increased with DULERA has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol fumarate than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

DULERA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. DULERA has not been studied in patients with acutely deteriorating asthma. The initiation of DULERA in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of DULERA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of DULERA.

DULERA is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not DULERA, should be used to relieve acute symptoms such as shortness of breath. When prescribing DULERA, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of DULERA.

When beginning treatment with DULERA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of DULERA and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, DULERA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using DULERA should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma.

5.4 Local Effects

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* have occurred in patients treated with DULERA. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while remaining on treatment with DULERA therapy, but at times therapy with DULERA may need to be interrupted. Advise patients to rinse the mouth after inhalation of DULERA.

5.5 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals.

Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

DULERA should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.6 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to DULERA because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although DULERA may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to DULERA. Lung function (FEV1 or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to DULERA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

5.7 Hypercorticism and Adrenal Suppression

Mometasone furoate, a component of DULERA, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since mometasone furoate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of DULERA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with DULERA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when mometasone furoate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of DULERA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of DULERA with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone furoate may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms

DULERA may produce inhalation induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If inhalation induced bronchospasm occurs, it should be treated immediately with an inhaled, short-acting inhaled bronchodilator. DULERA should be discontinued immediately and alternative therapy instituted.

5.10 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of DULERA, as demonstrated by cases of urticaria, flushing, allergic dermatitis, and bronchospasm.

5.11 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Therefore, DULERA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol fumarate, a component of DULERA, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of DULERA at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.12 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone furoate, one of the components of DULERA. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

In a 2-year double-blind study in 103 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 85%-88% predicted), treatment with mometasone furoate dry powder inhaler 200 mcg twice daily resulted in significant reductions in lumbar spine (LS) BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.015 (-1.43%) for the mometasone furoate group compared to 0.002 (0.25%) for the placebo group. In another 2-year double-blind study in 87 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 82%-83% predicted), treatment with mometasone furoate 400 mcg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the mometasone furoate group compared to -0.006 (-0.43%) for the placebo group.

5.13 Effect on Growth

Orally inhaled corticosteroids, including DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving DULERA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Use in Specific Populations (8.4)]*.

5.14 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported following the use of long-term administration of inhaled corticosteroids, including mometasone furoate, a component of DULERA. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts *[see Adverse Reactions (6)]*.

5.15 Coexisting Conditions

DULERA, like other medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.16 Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with DULERA at recommended doses.

6 ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1)]*.

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Immunosuppression *[see Warnings and Precautions (5.5)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.7)]*
- Growth effects in pediatrics *[see Warnings and Precautions (5.13)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.14)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The safety data described below is based on 3 clinical trials which randomized 1913 patients 12 years of age and older with asthma, including 679 patients exposed to DULERA for 12 to 26 weeks and 271 patients exposed for 1 year. DULERA was studied in two placebo- and active-controlled trials (n=781 and n=728, respectively) and in a long term 52-week safety trial (n=404). In the 12 to 26-week clinical trials, the population was 12 to 84 years of age, 41% male and 59% female, 73% Caucasians, 27% non-Caucasians. Patients received two inhalations twice daily of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol MDI (5 mcg) or placebo. In the long term 52-week active-comparator safety trial, the population was 12 years to 75 years of age with asthma, 37% male and 63% female, 47% Caucasians, 53% non-Caucasians and received two inhalations twice daily of DULERA 100 mcg/5 mcg or 200 mcg/5 mcg, or an active comparator.

The incidence of treatment emergent adverse reactions associated with DULERA in Table 2 below is based upon pooled data from 2 clinical trials 12 to 26-week in duration in patients 12 years and older treated with two inhalations twice daily of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol MDI (5mcg) or placebo.

Table 2: Treatment-emergent adverse reactions in DULERA groups occurring at an incidence of ≥3% and more commonly than placebo

Adverse Reactions	DULERA*		Mometasone Furoate*		Formoterol*	Placebo*
	100 mcg/5 mcg n=424 n (%)	200 mcg/5 mcg n=255 n (%)	100 mcg n=192 n (%)	200 mcg n=240 n (%)	5 mcg n=202 n (%)	n=196 n (%)
Nasopharyngitis	20 (4.7)	12 (4.7)	15 (7.8)	13 (5.4)	13 (6.4)	7 (3.6)
Sinusitis	14 (3.3)	5 (2.0)	6 (3.1)	4 (1.7)	7 (3.5)	2 (1.0)
Headache	19 (4.5)	5 (2.0)	10 (5.2)	8 (3.3)	6 (3.0)	7 (3.6)
Average Duration of Exposure (days)	116	81	165	79	131	138

*All treatments were administered as two inhalations twice daily.

Oral candidiasis has been reported in clinical trials at an incidence of 0.7% in patients using DULERA 100 mcg/5 mcg, 0.8 % in patients using DULERA 200 mcg/5 mcg and 0.5 % in the placebo group.

Long Term Clinical Trial Experience

In a long term safety trial in patients 12 years and older treated for 52 weeks with DULERA 100 mcg/5 mcg (n=141), DULERA 200 mcg/5 mcg (n=130) or an active comparator (n=133), safety outcomes in general were similar to those observed in the shorter 12 to 26 week controlled trials. No asthma-related deaths were observed. Dysphonia was observed at a higher frequency in the longer term treatment trial at a reported incidence of 7/141 (5%) patients receiving DULERA 100 mcg/5 mcg and 5/130 (3.8%) patients receiving DULERA 200 mcg/5 mcg. No clinically significant changes in blood chemistry, hematology, or ECG were observed.

7 DRUG INTERACTIONS

In clinical trials, concurrent administration of DULERA and other drugs, such as short-acting beta$_2$-agonist and intranasal corticosteroids have not resulted in an increased frequency of adverse drug reactions. No formal drug interaction studies have been performed with DULERA. The drug interactions of the combination are expected to reflect those of the individual components.

7.1 Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including mometasone furoate, a component of DULERA, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally inhaled mometasone furoate increased. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone furoate. Caution should be exercised when considering the coadministration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]*.

7.2 Adrenergic agents

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol, a component of DULERA, may be potentiated.

7.3 Xanthine derivatives

Concomitant treatment with xanthine derivatives may potentiate any hypokalemic effect of formoterol, a component of DULERA.

7.4 Diuretics

Concomitant treatment with diuretics may potentiate the possible hypokalemic effect of adrenergic agonists. The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of DULERA with non-potassium sparing diuretics.

7.5 Monoamine oxidase inhibitors, tricyclic antidepressants, and drugs known to prolong the QTc interval

DULERA should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of DULERA, on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.6 Beta-adrenergic receptor antagonists

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta$_2$-agonists, such as formoterol, a component of DULERA, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

DULERA: Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of DULERA, mometasone furoate only or formoterol fumarate only in pregnant women. Animal reproduction studies of mometasone furoate and formoterol in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human response, DULERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mometasone Furoate: Teratogenic Effects

When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations and decreased fetal growth (measured by lower fetal weights and/or delayed ossification). Dystocia and related complications were also observed when

mometasone furoate was administered to rats late in gestation. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

In a mouse reproduction study, subcutaneous mometasone furoate produced cleft palate at approximately one-third of the maximum recommended daily human dose (MRHD) on a mcg/m^2 basis and decreased fetal survival at approximately 1 time the MRHD. No toxicity was observed at approximately one-tenth of the MRHD on a mcg/m^2 basis.

In a rat reproduction study, mometasone furoate produced umbilical hernia at topical dermal doses approximately 6 times the MRHD on a mcg/m^2 basis and delays in ossification at approximately 3 times the MRHD on a mcg/m^2 basis.

In another study, rats received subcutaneous doses of mometasone furoate throughout pregnancy or late in gestation. Treated animals had prolonged and difficult labor, fewer live births, lower birth weight, and reduced early pup survival at a dose that was approximately 8 times the MRHD on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD on an AUC basis.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses approximately 3 times the MRHD on a mcg/m^2 basis. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at a dose less than the MRHD based on AUC. At a dose approximately 2 times the MRHD based on AUC, most litters were aborted or resorbed *[see Nonclinical Toxicology (13.2)]*.

Nonteratogenic Effects:
Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Infants born to mothers taking substantial corticosteroid doses during pregnancy should be monitored for signs of hypoadrenalism.

Formoterol Fumarate: Teratogenic Effects
Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of approximately 80 times the MRHD on a mcg/m^2 basis and above delayed ossification of the fetus, and doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of approximately 80 times the MRHD on a mcg/m^2 basis.

In another testing laboratory, formoterol was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses approximately 1,200 times and greater than the MRHD on a mcg/m^2 basis. Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose approximately 6,100 times the MRHD on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to approximately 500 times the MRHD on a mcg/m^2 basis. Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 49,000 times the MRHD on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to approximately 3,000 times the MRHD on a mcg/m^2 basis *[see Nonclinical Toxicology (13.2)]*.

8.2 Labor and Delivery
There are no adequate and well-controlled human studies that have studied the effects of DULERA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, DULERA should be used during labor only if the potential benefit justifies the potential risk *[see Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers
DULERA: It is not known whether DULERA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DULERA is administered to a nursing woman.

Since there are no data from well-controlled human studies on the use of DULERA on nursing mothers, based on data for the individual components, a decision should be made whether to discontinue nursing or to discontinue DULERA, taking into account the importance of DULERA to the mother.

Mometasone Furoate: It is not known if mometasone furoate is excreted in human milk. However, other corticosteroids are excreted in human milk.

Formoterol Fumarate: In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

8.4 Pediatric Use
The safety and effectiveness of DULERA have been established in patients 12 years of age and older in 3 clinical trials up to 52 weeks in duration. In the 3 clinical trials, 101 patients 12 to 17 years of age were treated with DULERA. Patients in this age-group demonstrated efficacy results similar to those observed in patients 18 years of age and older. There were no obvious differences in the type or frequency of adverse drug reactions reported in this age group compared to patients 18 years of age and older. Similar efficacy and safety results were observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use
A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

8.6 Hepatic Impairment
Concentrations of mometasone furoate appear to increase with severity of hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Signs and Symptoms
DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

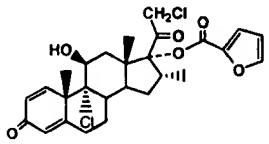
10.2 Treatment
DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such

medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION

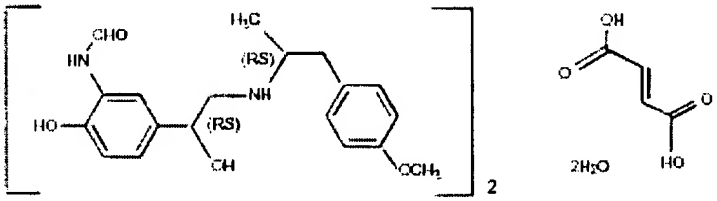
DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg, are combinations of mometasone furoate and formoterol fumarate dihydrate for oral inhalation only.

One active component of DULERA is mometasone furoate, a corticosteroid having the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) with the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight 521.44. It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone.

One active component of DULERA is formoterol fumarate dihydrate, a racemate. Formoterol fumarate dihydrate is a selective $beta_2$-adrenergic bronchodilator having the chemical name of (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate with the following chemical structure:



Formoterol fumarate dihydrate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate dihydrate is a white to yellowish powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

Each DULERA 100 mcg/5 mcg and 200 mcg/5 mcg is a hydrofluoroalkane (HFA-227) propelled pressurized metered dose inhaler containing sufficient amount of drug for 120 inhalations *[see How Supplied/Storage and Handling (16)]*. After priming, each actuation of the inhaler delivers 115 or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers 100 or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. DULERA also contains anhydrous alcohol as a cosolvent and oleic acid as a surfactant.

DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the mechanisms of actions described below for the individual components apply to DULERA. These drugs represent two different classes of medications (a synthetic corticosteroid and a selective long-acting $beta_2$-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Mometasone furoate: Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in

inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

Formoterol fumarate: Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

12.2 Pharmacodynamics

Cardiovascular Effects:

DULERA:

In a single dose, double blind placebo controlled crossover trial in 25 patients with asthma, single dose treatment of 10 mcg formoterol fumarate in combination with 400 mcg of mometasone furoate delivered via DULERA 200 mcg/5 mcg were compared to formoterol fumarate 10 mcg MDI, formoterol fumarate 12 mcg dry powder inhaler (DPI; nominal dose of formoterol fumarate delivered 10 mcg), or placebo. The degree of bronchodilation at 12 hours after dosing with DULERA was similar to formoterol fumarate delivered alone via MDI or DPI.

ECGs and blood samples for glucose and potassium were obtained prior to dosing and post dose. No downward trend in serum potassium was observed and values were within the normal range and appeared to be similar across all treatments over the 12 hour period. Mean blood glucose appeared similar across all groups for each time point. There was no evidence of significant hypokalemia or hyperglycemia in response to formoterol treatment.

No relevant changes in heart rate or changes in ECG data were observed with DULERA in the trial. No patients had a QTcB (QTc corrected by Bazett's formula) $\geq$500 msec during treatment.

In a single dose crossover trial involving 24 healthy subjects, single dose of formoterol fumarate 10, 20, or 40 mcg in combination with 400 mcg of mometasone furoate delivered via DULERA were evaluated for safety (ECG, blood potassium and glucose changes). ECGs and blood samples for glucose and potassium were obtained at baseline and post dose. Decrease in mean serum potassium was similar across all three treatment groups (approximately 0.3 mmol/L) and values were within the normal range. No clinically significant increases in mean blood glucose values or heart rate were observed. No subjects had a QTcB >500 msec during treatment.

Three active- and placebo-controlled trials (study duration ranging from 12, 26, and 52 weeks) evaluated 1913 patients 12 years of age and older with asthma. No clinically meaningful changes were observed in potassium and glucose values, vital signs, or ECG parameters in patients receiving DULERA.

HPA Axis Effects:

The effects of inhaled mometasone furoate administered via DULERA on adrenal function were evaluated in two clinical trials in patients with asthma. HPA-axis function was assessed by 24-hour plasma cortisol AUC. Although both these trials have open-label design and contain small number of subjects per treatment arm, results from these trials taken together demonstrated suppression of 24-hour plasma cortisol AUC for DULERA 200 mcg/5 mcg compared to placebo consistent with the known systemic effects of inhaled corticosteroid.

In a 42-day, open-label, placebo and active-controlled study 60 patients with asthma 18 years of age and older were randomized to receive two inhalations twice daily of 1 of the following treatments: DULERA 100 mcg/5 mcg, DULERA 200 mcg/5 mcg, fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg, or placebo. At Day 42, the mean change from baseline plasma cortisol AUC (0-24 hr) was 8%, 22% and 34% lower compared to placebo for the DULERA 100 mcg/5 mcg (n=13), DULERA 200 mcg/5 mcg (n=15) and fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg (n=16) treatment groups, respectively.

In a 52-week, open-label safety study, primary analysis of the plasma cortisol 24-hour AUC was performed on 57 patients with asthma who received 2 inhalations twice daily of DULERA 100 mcg/5 mcg, DULERA 200 mcg/5 mcg, fluticasone propionate/salmeterol xinafoate 250/50, or fluticasone propionate/salmeterol xinafoate 500/50. At Week 52, the mean plasma cortisol AUC (0-24 hr) was 2.2%, 29.6%, 16.7%, and 32.2% lower from baseline for the DULERA 100 mcg/5 mcg (n=18), DULERA 200 mcg/5 mcg (n=20), fluticasone propionate/salmeterol xinafoate 250/50 mcg (n=8), and fluticasone propionate/salmeterol xinafoate 500/50 mcg (n=11) treatment groups, respectively.

Other Mometasone Products

HPA Axis Effects:

The potential effect of mometasone furoate via a dry powder inhaler (DPI) on the HPA axis was assessed in a 29-day study. A total of 64 adult patients with mild to moderate asthma were randomized to one of 4 treatment groups: mometasone furoate DPI 440 mcg twice daily, mometasone furoate DPI 880 mcg twice daily, oral prednisone 10 mg once daily, or placebo. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dl for the mometasone furoate DPI 440 mcg twice daily group and 20.8 mcg/dl for the mometasone furoate DPI 880 mcg twice daily group, compared to 14.5 mcg/dl for the oral prednisone 10 mg group and 25 mcg/dl for the placebo group. The difference between mometasone furoate DPI 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

12.3 Pharmacokinetics

Absorption

Mometasone furoate:

Healthy Subjects: The systemic exposures to mometasone furoate from DULERA versus mometasone furoate delivered via DPI were compared. Following oral inhalation of single and multiple doses of the DULERA, mometasone furoate was absorbed in healthy subjects with median Tmax values ranging from 0.50 to 4 hours. Following single-dose administration of higher than recommended dose of DULERA (4 inhalations of DULERA 200 mcg/5 mcg) in healthy subjects, the arithmetic mean (CV%) Cmax and AUC (0-12h) values for MF were 67.8 (49) pg/mL and 650 (51) pg.hr/mL, respectively while the corresponding estimates following 5 days of BID dosing of DULERA 800 mcg/20 mcg were 241 (36) pg/mL and 2200 (35) pg.hr/mL. Exposure to mometasone furoate increased with increasing inhaled dose of DULERA 100 mcg/5 mcg to 200 mcg/5 mcg. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of mometasone furoate is negligible (<1%).

The above study demonstrated that the systemic exposure to mometasone furoate (based on AUC) was approximately 52% and 25% lower on Day 1 and Day 5, respectively, following DULERA administration compared to mometasone furoate via a DPI.

Asthma Patients: Following oral inhalation of single and multiple doses of the DULERA, mometasone furoate was absorbed in asthma patients with median Tmax values ranging from 1 to 2 hours. Following single-dose administration of DULERA 400 mcg/10 mcg, the arithmetic mean (CV%) Cmax and AUC (0-12h) values for MF were 20 (88) pg/mL and 170 (94) pg.hr/mL, respectively while the corresponding estimates following BID dosing of DULERA 400 mcg/10 mcg at steady-state were 60 (36) pg/mL and 577 (40) pg.hr/mL.

Formoterol fumarate:

Healthy Subjects: When DULERA was administered to healthy subjects, formoterol was absorbed with median Tmax values ranging from 0.167 to 0.5 hour. In a single-dose study with DULERA 400 mcg/10 mcg in healthy subjects, arithmetic mean (CV%) Cmax and AUC for formoterol were 15 (50) pmol/L and 81 (51) pmol*h/L, respectively. Over the dose range of 10 to 40 mcg for formoterol from DULERA, the exposure to formoterol was dose proportional.

Asthma Patients: When DULERA was administered to patients with asthma, formoterol was absorbed with median Tmax values ranging from 0.58 to 1.97 hours. In a single-dose study with DULERA 400 mcg/10 mcg in patients with asthma, arithmetic mean (CV%) Cmax and AUC (0-12h) for formoterol were 22 (29) pmol/L and 125 (42) pmol*h/L, respectively. Following multiple-dose administration of DULERA 400 mcg/10 mcg, the steady-state arithmetic mean (CV%) Cmax and AUC (0-12h) for formoterol were 41 (59) pmol/L and 226 (54) pmol*hr/L.

Distribution

Mometasone furoate: Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg

dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean steady-state volume of distribution of 152 liters. The *in vitro* protein binding for mometasone furoate was reported to be 98 to 99% (in a concentration range of 5 to 500 ng/mL).

Formoterol fumarate: The binding of formoterol to human plasma proteins in vitro was 61% to 64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31% to 38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Metabolism
Mometasone furoate: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In-vitro studies have confirmed the primary role of human liver cytochrome P-450 3A4 (CYP3A4) in the metabolism of this compound, however, no major metabolites were identified. Human liver CYP3A4 metabolizes mometasone furoate to 6-beta hydroxy mometasone furoate.

Formoterol fumarate: Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion
Mometasone furoate: Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine. Absorbed mometasone furoate is cleared from plasma at a rate of approximately 12.5 mL/min/kg, independent of dose. The effective t½ for mometasone furoate following inhalation with DULERA was 25 hours in healthy subjects and in patients with asthma.

Formoterol fumarate: Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59% to 62% of the radioactivity was eliminated in the urine and 32% to 34% in the feces over a period of 104 hours. In an oral inhalation study with DULERA, renal clearance of formoterol from the blood was 217 mL/min. In single-dose studies, the mean t½ values for formoterol in plasma were 9.1 hours and 10.8 hours from the urinary excretion data. The accumulation of formoterol in plasma after multiple dose administration was consistent with the increase expected with a drug having a terminal t½ of 9 to 11 hour.

Following single inhaled doses ranging from 10 to 40 mcg to healthy subjects from the MFF MDI, 6.2% to 6.8% of the formoterol dose was excreted in urine unchanged. The (R,R) and (S,S)-enantiomers accounted, respectively, for 37% and 63% of the formoterol recovered in urine. From urinary excretion rates measured in healthy subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13 and 9.5 hours, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied.

Special Populations
Hepatic/Renal Impairment: There are no data regarding the specific use of DULERA in patients with hepatic or renal impairment.

A study evaluating the administration of a single inhaled dose of 400 mcg mometasone furoate by a dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.

Gender and Race: Specific studies to examine the effects of gender and race on the pharmacokinetics of DULERA have not been specifically studied.

Geriatrics: The pharmacokinetics of DULERA have not been specifically studied in the elderly population.

Drug-Drug Interactions
A single-dose crossover study was conducted to compare the pharmacokinetics of 4 inhalations of the following: mometasone furoate MDI, formoterol MDI, DULERA (mometasone furoate/formoterol fumarate MDI), and mometasone furoate MDI plus formoterol

fumarate MDI administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of DULERA.

Inhibitors of Cytochrome P450 Enzymes: Ketoconazole: In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg delivered by a dry powder inhaler was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211-324 pcg/mL. Mometasone furoate plasma levels appeared to increase and plasma cortisol levels appeared to decrease upon concomitant administration of ketoconazole.

Specific drug-drug interaction studies with formoterol have not been performed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mometasone furoate: In a 2-year carcinogenicity study in Sprague Dawley® rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 14 times the MRHD on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 9 times the MRHD on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 8 times the MRHD on an AUC basis).

Formoterol fumarate: The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 265 times human exposure at the MRHD). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 27 times human exposure at the MRHD). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 350 times human exposure at the MRHD) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 35 times human exposure at the MRHD). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 14 times human exposure at the MRHD). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1200 times the MRHD on a mcg/m2 basis).

13.2 Animal Toxicology and/or Pharmacology

Animal Pharmacology

Formoterol fumarate: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Reproductive Toxicology Studies

Mometasone furoate: In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (approximately 1/3 of the maximum recommended human dose MRHD on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the MRHD on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (approximately one-tenth of the MRHD on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the MRHD on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the MRHD on a mcg/m^2 basis) produced delays in ossification, but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times the MRHD on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 4 times the MRHD on an AUC basis).

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the MRHD on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the MRHD on an area under the curve [AUC] basis). At 2800 mcg/kg (approximately 2 times the MRHD on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the MRHD on an AUC basis).

Formoterol fumarate: Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 80 times the MRHD on a mcg/m^2 basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 80 times the MRHD on a mcg/m^2 basis).

In another testing laboratory, formoterol fumarate was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1,200 times greater than the MRHD on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose of 15 mg/kg/day (approximately 6,100 times the MRHD on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the MRHD on a mcg/m^2 basis). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose of 60 mg/kg (approximately 49,000 times the MRHD on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3,000 times the MRHD on a mcg/m^2 basis).

14 CLINICAL STUDIES

14.1 Asthma

The safety and efficacy of DULERA were demonstrated in two randomized, double-blind, parallel group, multicenter clinical trials of 12 to 26 weeks in duration involving 1509 patients 12 years of age and older with persistent asthma uncontrolled on medium or high dose inhaled corticosteroids (baseline FEV1 means of 66% to 73% of predicted normal). These studies included a 2 to 3-week run-in period with mometasone furoate to establish a certain level of asthma control. One clinical trial compared DULERA to placebo and the individual components, mometasone furoate and formoterol (Trial 1) and one clinical trial compared two different strengths of DULERA to mometasone furoate alone (Trial 2).

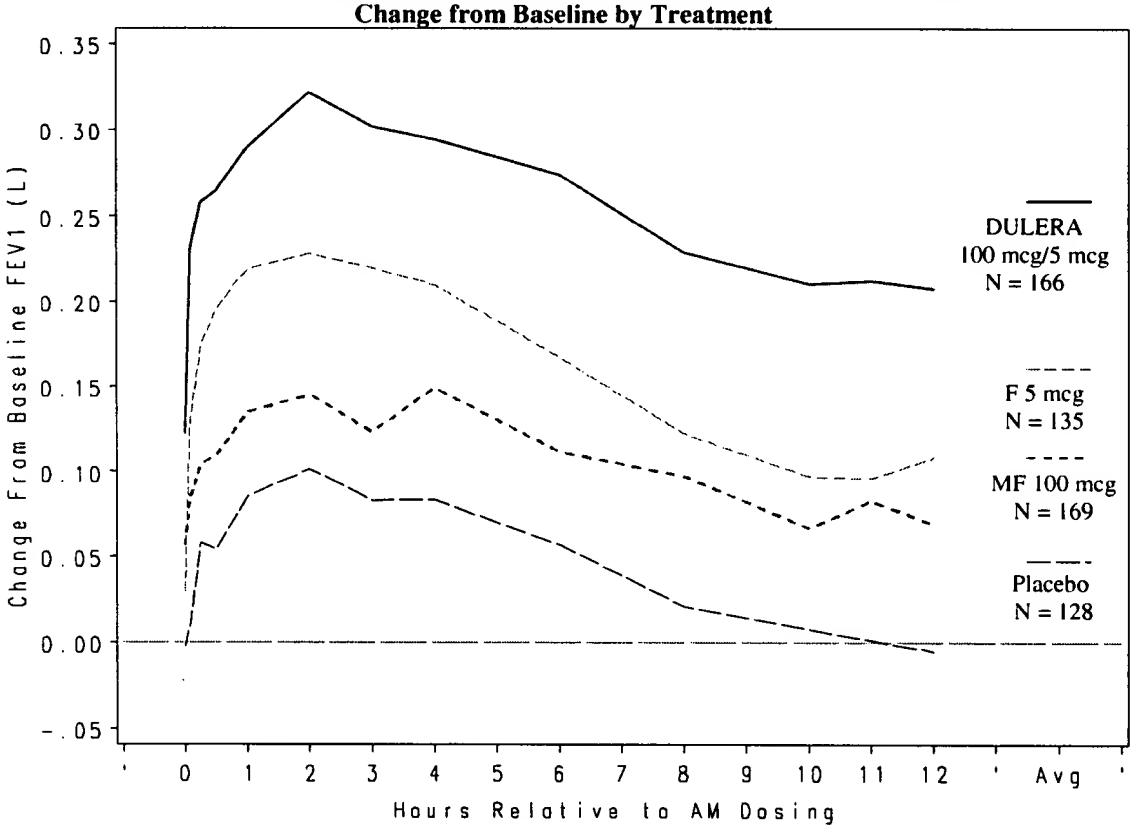
Trial 1: Clinical Trial with DULERA 100 mcg/5 mcg

This 26-week, placebo controlled trial evaluated 781 patients 12 years of age and older comparing DULERA 100 mcg/5 mcg (n=191 patients), mometasone furoate 100 mcg (n=192 patients), formoterol fumarate 5 mcg (n=202 patients) and placebo (n=196 patients); each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. This study included a 2 to 3-week run-in period with mometasone furoate 100 mcg, 2 inhalations twice daily. This trial included patients ranging from 12 to 76 years of age, 41% male and 59% female, and 72% Caucasian and 28% non-Caucasian. Patients had persistent asthma and were not well controlled on medium dose of inhaled corticosteroids prior to randomization. All treatment groups were balanced with regard to baseline characteristics. Mean FEV1 and mean percent predicted FEV1 were similar among all treatment groups (2.33 L, 73%). Eight (4%) patients receiving DULERA 100 mcg/5 mcg, 13 (7%) patients receiving mometasone furoate 100 mcg, 47 (23%) patients receiving formoterol fumarate 5 mcg and 46 (23%) patients receiving placebo discontinued the study early due to treatment failure.

FEV1 AUC (0-12hr) was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component to DULERA. Patients receiving DULERA 100 mcg/5 mcg had significantly higher increases from baseline at Week 12 in mean FEV1 AUC (0-12 hr) compared to mometasone furoate 100 mcg (the primary treatment comparison) and vs. placebo (both p<0.001) (Figure 1). These differences were maintained through Week 26. Figure 1 shows the change from baseline post-dose serial FEV1 evaluations in Trial 1.

Figure 1

TRIAL 1 - DULERA 100 mcg/5 mcg - FEV1 Serial Evaluations for Observed Cases at Week 12
Change from Baseline by Treatment



MF = Mometasone furoate
F = Formoterol fumarate
Mean FEV1 over 12 hours at Week 12 (shown as AVG)

Clinically judged deteriorations in asthma or reductions in lung function were assessed as another primary endpoint to evaluate the contribution of mometasone furoate 100 mcg to DULERA 100 mcg/5 mcg (primary treatment comparison DULERA vs. formoterol). Deteriorations in asthma were defined as any of the following: a 20% decrease in FEV1; a 30% decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Fewer patients who received DULERA 100 mcg/5 mcg reported an event compared to patients who received formoterol 5 mcg (p<0.001).

Table 3: Trial 1 - Clinically judged deterioration in asthma or reduction in lung function*

	DULERA 100 mcg/ 5 mcg§ (n=191)	Mometasone furoate 100 mcg§ (n=192)	Formoterol 5 mcg§ (n=202)	Placebo§ (n=196)
Clinically judged deterioration in asthma or reduction in lung function*	58 (30%)	65 (34%)	109 (54%)	109 (56%)
Decrease in FEV1**	18 (9%)	19 (10%)	31 (15%)	41 (21%)

Decrease in PEF†	37 (19%)	41 (21%)	62 (31%)	61 (31%)
Emergency treatment	0	1 (<1%)	4 (2%)	1 (<1%)
Hospitalization	1 (<1%)	0	0	0
Treatment with excluded asthma medication‡	2 (1%)	4 (2%)	17 (8%)	8 (4%)

*Includes only the first event day for each patient. Patients could have experienced more than one event criterion.
**Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication)
†Decrease in AM or PM peak expiratory flow (PEF) on 2 or more consecutive days below the treatment period stability limit (defined as 70% of the AM or PM PEF obtained over the last 7 days of the run-in period)
‡Thirty patients received glucocorticosteroids; 1 patient received formoterol via dry powder inhaler in the Formoterol 5 mcg group.
§Two inhalations, twice daily.

The change in mean trough FEV1 from baseline to Week 12 was assessed as another endpoint to evaluate the contribution of mometasone furoate 100 mcg to DULERA 100 mcg/5 mcg. A significantly greater increase in mean trough FEV1 was observed for DULERA 100 mcg/5 mcg compared to formoterol 5 mcg (the primary treatment comparison) as well as to placebo (Table 4).

Table 4: Trial 1 – Change in trough FEV1 from baseline to Week 12

Treatment arm	N	Baseline (L)	Change from baseline at Week 12 (L)	Treatment difference from placebo (L)	P-value vs. placebo	P-value vs. formoterol
DULERA 100 mcg/5 mcg	167	2.33	0.13	0.18	<0.001	<0.001
Mometasone furoate 100 mcg	175	2.36	0.07	0.12	<0.001	0.058
Formoterol fumarate 5 mcg	141	2.29	0.00	0.05	0.170	
Placebo	145	2.30	-0.05			

LS means and p-values are from Week 12 estimates of a longitudinal analysis model.

The effect of DULERA 100 mcg/5 mcg, two inhalations twice daily on selected secondary efficacy endpoints, including proportion of nights with nocturnal awakenings (-60% vs. -15%), change in total rescue medication use (-0.6 vs. +1.1 puffs/day), change in morning peak flow (+18.1 vs. -28.4 L/min) and evening peak flow (+10.8 vs. -32.1 L/min) further supports the efficacy of DULERA 100 mcg/5 mcg compared to placebo.

The subjective impact of asthma on patients' health-related quality of life was evaluated by the Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). A change from baseline >0.5 points is considered a clinically meaningful improvement. The mean difference in AQLQ between patients receiving DULERA 100 mcg/5 mcg and placebo was 0.5 [95% CI 0.32, 0.68].

Trial 2: Clinical Trial With DULERA 200 mcg/5 mcg

This 12-week double-blind trial evaluated 728 patients 12 years of age and older comparing DULERA 200 mcg/5 mcg (n=255 patients) with DULERA 100 mcg/5 mcg (n=233 patients) and mometasone furoate 200 mcg (n=240 patients), each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. This trial included a 2 to 3-week run-in period with mometasone furoate 200 mcg, 2 inhalations twice daily. Patients had persistent asthma and were uncontrolled on high dose inhaled corticosteroids prior to study entry. All treatment groups were balanced with regard to baseline characteristics. This trial included patients ranging from 12 to 84 years of age, 44% male and 56% female, and 89% Caucasian and 11% non-Caucasian. Mean FEV1 and mean percent predicted FEV1 values were similar among all treatment groups (2.05 L, 66%). Eleven (5%) patients receiving DULERA 100 mcg/5 mcg, 8 (3%) patients receiving DULERA 200 mcg/5 mcg and 13 (5%) patients receiving mometasone furoate 200 mcg discontinued the trial early due to treatment failure.

The primary efficacy endpoint was the mean change in FEV1 AUC (0-12 hr) from baseline to Week 12. Patients receiving DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg had significantly greater increases from baseline at Day 1 in mean FEV1 AUC (0-12 hr) compared to mometasone furoate 200 mcg. The difference was maintained over 12 weeks of therapy.

Mean change in trough FEV1 from baseline to Week 12 was also assessed to evaluate the relative contribution of mometasone furoate to DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg (Table 5). A greater numerical increase in the mean trough FEV1 was observed for DULERA 200 mcg/5 mcg compared to DULERA 100 mcg/5 mcg and mometasone furoate 200 mcg.

Table 5: Trial 2 – Change in trough FEV1 from baseline to Week 12

Treatment arm	N	Baseline (L)	Change from baseline at Week 12 (L)
DULERA 100 mcg/5 mcg	**232**	**2.10**	**0.14**
DULERA 200 mcg/5 mcg	**255**	**2.05**	**0.19**
Mometasone furoate 200 mcg	**239**	**2.07**	**0.10**

Clinically judged deterioration in asthma or reduction in lung function was assessed as an additional endpoint. Fewer patients who received DULERA 200 mcg/5 mcg or DULERA 100/5 mcg compared to mometasone furoate 200 mcg alone reported an event, defined as in Trial 1 by any of the following: a 20% decrease in FEV1; a 30% decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol.

Table 6: Trial 2 - Clinically judged deterioration in asthma or reduction in lung function*

	DULERA 100 mcg/ 5 mcg§ (n=233)	DULERA 200 mcg/ 5 mcg§ (n=255)	Mometasone furoate 200 mcg§ (n=240)
Clinically judged deterioration in asthma or reduction in lung function*	29 (12%)	31 (12%)	44 (18%)
Decrease in FEV1**	23 (10%)	17 (7%)	33 (14%)
Decrease in PEF on two consecutive days†	2 (1%)	4 (2%)	3 (1%)
Emergency treatment	2 (1%)	1 (<1%)	1 (<1%)
Hospitalization	0	1 (<1%)	0
Treatment with excluded asthma medication‡	5 (2%)	8 (3%)	12 (5%)

*Includes only the first event day for each patient. Patients could have experienced more than one event criterion.
**Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication)
†Decrease in AM or PM peak expiratory flow (PEF) below the treatment period stability limit (defined as 70% of the AM or PM PEF obtained over the last 7 days of the run-in period)
‡Twenty four patients received glucocorticosteroids; 1 patient received albuterol in the DULERA 200 mcg / 5 mcg group.
§Two inhalations, twice daily.

Other Studies
In addition to Trial 1 and Trial 2, the safety and efficacy of the individual components, mometasone furoate MDI 100 mcg and 200 mcg, in comparison to placebo were demonstrated in three other, 12-week, placebo controlled trials which evaluated the mean change in FEV1 from baseline as a primary endpoint. The safety and efficacy of formoterol MDI 5 mcg alone in comparison to placebo was replicated in another 26-week trial that evaluated a lower dose of mometasone furoate MDI in combination with formoterol.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
DULERA is available in two strengths (Table 7):

Table 7

Package	NDC

DULERA 100 mcg/5 mcg	0085-7206-01
DULERA 200 mcg/5 mcg	0085-4610-01

Each strength is supplied as a pressurized aluminum canister that has a blue plastic actuator integrated with a dose counter and a blue dust cap. Each 120-inhalation canister has a net fill weight of 13 grams. Each canister is placed into a carton. Each carton contains 1 canister and a Medication Guide.

Initially the dose counter will display "124" actuations. After the initial priming with 4 actuations, the dose counter will read "120" and the inhaler is now ready for use.

16.2 Storage and Handling

The DULERA canister should only be used with the DULERA actuator. The DULERA actuator should not be used with any other inhalation drug product. Actuators from other products should not be used with the DULERA canister.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the canister has been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of actuations has been used (the dose counter will read "0").

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

For best results, the canister should be at room temperature before use. Shake well before using. Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

17 PATIENT COUNSELING INFORMATION

[See Medication Guide.]

17.1 Asthma-Related Death

[See Medication Guide.]

Patients should be informed that formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of DULERA, or other long-term asthma-control therapy mitigates or eliminates this risk *[see Warnings and Precautions (5.1)]*.

17.2 Not for Acute Symptoms

DULERA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).

Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta$_2$-agonist than usual

Patients should be advised not to increase the dose or frequency of DULERA. The daily dosage of DULERA should not exceed two inhalations twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. DULERA provides bronchodilation for up to 12 hours.

Patients should not stop or reduce DULERA therapy without physician/provider guidance since symptoms may recur after discontinuation *[see Warnings and Precautions (5.2)]*.

17.3 Do Not Use Additional Long-Acting Beta$_2$-Agonists

When patients are prescribed DULERA, other long-acting beta$_2$-agonists should not be used *[see Warnings and Precautions (5.3)]*.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy

while still continuing with DULERA therapy, but at times therapy with DULERA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised *[see Warnings and Precautions (5.4)]*.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex *[see Warnings and Precautions (5.5)]*.

Hypercorticism and Adrenal Suppression: Patients should be advised that DULERA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to DULERA *[see Warnings and Precautions (5.7)]*.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition *[see Warnings and Precautions (5.12)]*.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route *[see Warnings and Precautions (5.13)]*.

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered *[see Warnings and Precautions (5.14)]*.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed that treatment with $beta_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness *[see Warnings and Precautions (5.11)]*.

Manufactured by 3M Health Care Ltd., Loughborough, United Kingdom.
Manufactured for Schering Corporation, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889 USA.

EXHIBIT 9

BRIEF DESCRIPTION OF ACTIVITIES UNDERTAKEN BY SCHERING FOR Dulera (mometasone furoate/ formoterol fumarate) DURING THE REGULATORY REVIEW PERIOD

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
20-Mar-03	Submission of Pharmacology/Toxicology Briefing Package for Guidance Meeting	Briefing Package
11-Jun-03	Meeting (Type C) with DPADP and SPRI: toxicology requirements for proposed fixed dose combination	Meeting
15-Aug-03	Submissions of Pharmacology/Toxicology Briefing Package for Guidance Meeting	Briefing Package
26-Sep-03	Meeting (Type C) with DPADP and SPRI: toxicology requirements for proposed fixed dose combination	Teleconference
5-Oct-04	Submission of Clinical/Pharmacology Briefing Package for Guidance Meeting	Briefing package
3-Nov-04	Meeting (Type C) with DPADP and SPRI: clinical trial designs regarding monotherapy comparisons.	Meeting
24-Feb-06	Submission of Pre-IND Briefing Package for Guidance Meeting	Briefing Package
28-Mar-06	Meeting (Type B) with DPADP and SPRI: pre-IND discussion regarding clinical trial design and toxicology requirements.	Meeting
26-May-06	Submission of IND 70,283 to develop the combination of mometasone furoate/ formoterol fumarate including protocol P04431 12-week High Dose Study	IND application
9-Jun-06	Submission of response to FDA comments regarding IND 70,283: CMC requests	Response submitted to IND
5-Jul-06	Submission of Cross-Reference to Novartis IND 64,719	Letter
2-Aug-06	Submission of new investigators	IND Amendment
9-Aug-06	Submission of CMC Briefing Package for Guidance Meeting	Briefing Package
12-Sep-06	Meeting (Type C) with DPADP and SPRI: CMC requirements	Meeting
12-Oct-06	Submission of new protocol P04073 (26-Week Low Dose Study) and new investigators	IND Protocol Amendment
15-Nov-06	Submission of new investigators	IND Amendment
15-Dec-06	Submission of new investigators	IND Amendment
19-Jan-07	Submission of new protocol P04705 (Non-inferiority Study) and new investigators	IND Protocol Amendment
23-Feb-07	Submission of new protocol P03705 (HPA-Axis Function Study) and new investigators	IND Protocol Amendment
22-Mar-07	Submission of new investigators	IND Amendment

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
13-Apr-07	Submission of new protocol P03658 (PK Interaction Study) and new investigators	IND Protocol Amendment
17-May-07	Submission of new investigators	IND Amendment
11-Jun-07	Submission of new investigators	IND Amendment
12-Jul-07	Submission of new protocol P04689 (BA/Systemic Exposure Study)	IND Protocol Amendment
16-Jul-07	Submission of notification – partial halt to recruitment of women of child bearing potential, pending an amendment of the protocols (P04431, P04334, P04073, P04705)	Notification
30-Jul-07	Response to FDA question dated 1-Jun-07 re: P03658	Response submitted to IND
31-Jul-07	Submission of samples of Dose Counter and response to FDA feedback	IND Amendment and Response document
06-Aug-07	Submission of new investigators and updated investigator information	IND Amendment
27-Aug-07	Submission of Annual Report	IND Amendment
31-Aug-07	Submission of protocol amendment (P04431Am2, P04705Am1), new investigators and updated investigator information	IND Amendment
10-Sep-07	Notification of lifting of temporary, partial halt to recruitment	Notification
18-Sep-07	Submission of Protocol Concept for FDA Review (P05213)	IND Amendment
02-Oct-07	Submission of protocol amendment (P04334Am1, P04073Am1), new investigators and updated investigator information	IND Amendment
31-Oct-07	Submission of new protocol P05122 (eNO Study), new investigators, and updated investigator information	IND Amendment
04-Dec-07	Submission of new protocol P04703 (Dose Counter Study), new investigators and updated investigator information	IND Amendment
18-Dec-07	Submission of information amendment: CMC	IND Amendment
08-Jan-08	Submission of protocol amendment (P05122Am1), new investigators and updated investigator information	IND Amendment
17-Jan-08	Submission of Clinical Data Analysis Plan (DAP) for P04431	IND Amendment
21-Feb-08	Submission of information amendment: CMC	IND Amendment
25-Feb-08	Submission of CMC Briefing Package for Guidance Meeting	IND Amendment
25-Feb-08	Submission of new investigators and updated investigator information	IND Amendment
24-Mar-08	Submission of new investigators and updated investigator information	IND Amendment
21-Apr-08	Submission of new investigators and updated investigator information	IND Amendment
23-Apr-08	Meeting (Type C) with DPADP and SPRI: CMC requirements	Meeting
21-May-08	Submission of new investigators and updated investigator information	IND Amendment

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
25-Jul-08	Submission of information amendment: clinical DAP for P04073	IND Amendment
01-Aug-08	Submission of new investigators and updated investigator information	IND Amendment
14-Aug-08	Submission protocol amendments (P04703Am1, P05527Am1)	IND Protocol Amendment
27-Aug-08	Submission of Annual Report	IND Amendment
10-Sep-08	Submission of new investigators and updated investigator information	IND Amendment
30-Jun-08	Submission of new investigators and updated investigator information	IND Amendment
10-Sep-08	Notification of investigator of Clinical Study Sites in the Philippines	Notification
9-Oct-08	Submission of updated investigator information	IND Amendment
06-Nov-08	Submission of updated investigator information	IND Amendment
13-Nov-08	Submission of pre-NDA Briefing Package for Guidance Meeting	Briefing Package
9-Dec-08	Submission of new investigators and updated investigator information	IND Amendment
15-Dec-08	Meeting (Type B) with DPADP and SPRI: pre-NDA submission guidance	Meeting
15-Jan-09	Response to FDA questions dated 30-Oct-2008 re: CMC information	Response submitted to IND
13-Feb-09	Submission of new investigators and updated investigator information	IND Amendment
16-Mar-09	Request for Proprietary Name Review, Primary Name: Dulera	IND Amendment
06-Apr-09	Submission of new investigators and updated investigator information	IND Amendment
21-May-09	Submission of New Drug Application 22,518	New Drug Application
29-May-09	Submission to IND - Request for Proprietary Name Review, Primary Name: Dulera	IND Amendment
04-Jun-09	Submission of FORM FDA 3674	Submission to NDA
16-Jun-09	Response to FDA Request dated 15-Jun-09 re: activities at sites listed on 356h form and for letters of to the drug substance information	Response submitted to NDA
1-Jul-09	Submission of Sample Dulera Inhalers	Submission to NDA
16-Jul-09	Submission of Projected HFA usage	Submission to NDA
24-Jul-09	Response to FDA request for information dated 20-Jul-09 re: CMC	Response submitted to NDA
12-Aug-09	Response to FDA Labeling Comments dated 4-Aug-09: submission of revised draft labeling	Response submitted to NDA
26-Aug-09	Submission of Patent Information	Submission to NDA
27-Aug-09	Submission to IND - Annual Report	IND Amendment
04-Sep-09	Response to FDA Request for information dated 4-Aug-09 re: Clinical, Clinical Pharmacology, Statistics, and CMC	Response submitted to NDA
22-Sep-09	Submission of 4 month Safety Update Report	Submission to NDA

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
29-Oct-09	Submission of amendment to pending application: minor revisions to Module 3 Quality	Submission to NDA
04-Nov-09	Notification of combined companies through reverse merger.	Notification
10-Nov-09	Notification of correspondence provided in response to the Sponsor-Monitor Inspection	Notification
13-Nov-09	Response to FDA request for information dated 13-Oct-09 re: microbial limits testing	Response submitted to NDA
25-Nov-09	Response to FDA request for information dated 26-Oct-09 re: CMC information	Response submitted to NDA
11-Jan-10	Response to FDA request for information dated 23-Dec-09 re: spirometry testing procedures	Response submitted to NDA
14-Jan-10	Response to FDA request for information dated 22-Dec-09 re: CMC information	Response submitted to NDA
22-Jan-10	Response to FDA request for information dated 19-Jan-10 re: Clinical Data Listings	Response submitted to NDA
26-Jan-10	Meeting between Merck and DPADP: discuss ongoing review of application	Meeting
29-Jan-10	Response to FDA request for information dated 19-Jan-10 re: CMC information	Response submitted to NDA
03-Feb-10	Submission of Method Validation Kit	Submission to NDA
04-Feb-10	Submission to IND – final Clinical Study Report P05122	IND Amendment
12-Feb-10	Response to FDA request for information dated 27-Jan-10 re: Pediatric Plan	Response submitted to NDA
16-Feb-10	Response to FDA 74-Day letter – further clarify clinical issues discussed 26-Jan-10	Response submitted to NDA
05-Mar-10	Response to FDA request for information dated 19-Feb-10 re: CMC information	Response submitted to NDA
05-Mar-10	Response to FDA labeling comments dated 18-Feb-10 and submission of revised draft labeling and proposed Risk Evaluation and Mitigation Strategy (REMS)	Response submitted to NDA
16-Mar-10	Submission of amendment to pending application: minor revisions to Module 3 Quality	Submission to NDA
20-May-10	Meeting between Merck and DPADP: discuss Post-Marketing Requirements (PMR) and ongoing review of application	Meeting
21-May-10	Response to FDA Request of Information dated 18-May-10 re: Clinical Pharmacology information	Response submitted to NDA
26-May-10	Response to FDA request for Information dated 17-May-10 re: CMC information	Response submitted to NDA

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
04-Jun-10	Meeting between Merck and DPADP: USPI and Medication Guide Discussions	Meeting
10-Jun-10	Response to FDA request for information dated 4-Jun-10 re: Clinical information	Response via email and submission to NDA
10-Jun-10	Response to FDA request for information dated 4-Jun-10 re: REMS	Response via email and submission to NDA
10-Jun-10	Response to FDA request for information dated 26-May-10 re: PMR	Response via email and submission to NDA
11-Jun-10	Response to FDA request for information dated 8-Jun-10 and 10-Jun-10 re: Nonclinical information	Response via email and submission to NDA
11-Jun-10	Response to FDA request for information dated 10-Jun-10 re: Clinical information	Response via email and submission to NDA
11-Jun-10	Response to FDA request for information dated 11-Jun-10 re: Pediatric Plan	Response via email and submission to NDA
15-Jun-10	Response to FDA request for information dated 11-Jun-10 re: Medication Guide	Response via email and submission to NDA
14-Jun-10 and 18-Jun-10	Response to FDA request for information dated 11-Jun-10 re: REMS	Response via email and submission to NDA
7-Jun-10 and 18-Jun-10	Response to FDA label comments dated 25-May-10 re: Label	Response via email and submission to NDA
17-Jun-10 and 18-Jun-10	Response to FDA request for information dated 11-Jun-10 re: REMS	Response via email and submission to NDA
17-Jun-10 and 18-Jun-10	Response to FDA labeling comments dated 15-Jun-10 re: USPI and Medication Guide	Response via email and submission to NDA
17-Jun-10 and 18-Jun-10	Response to FDA request for information dated 16-Jun-10 re: Final carton and container	Response via email and submission to NDA
18-Jun-10 and 21-Jun-10	General Correspondence: carton and canister label distribution	Notification
18-Jun-10 and 21-Jun-10	Response to FDA request for information dated 18-Jun-10 re: REMS	Response via email and submission to NDA
21-Jun-10	Response to FDA request for information dated 18-Jun-10 re: REMS	Response via email and submission to NDA
21-Jun-10	Response to FDA labeling comments dated 18-Jun-10 re: USPI and Medication Guide	Response via email and submission to NDA
22-Jun-10	Response to FDA request for information dated 21-Jun-10 re: REMS	Response via email and submission to NDA
22-Jun-10	Response to FDA request for information dated 22-Jun-10 re: REMS	Response via email and submission to NDA

Submission Date	Correspondence and notable submissions made to the USFDA, Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), Office of Drug Evaluation II, Division of Pulmonary and Allergy Drug Products, concerning DULERA (mometasone furoate / formoterol fumarate) IND 70,283 and NDA 22-518	Type of Correspondence
23-Jun-10	Response to FDA request for information dated 21-Jun-10 re: additional clinical information not vital to action on application	Response via email and submission to NDA
30-Jun-10	Submission of final SPL Labeling for approved application 22-518	Submission to NDA
21-Jul-10	Submission of Patent Information	Submission to NDA
6-Aug-10	Submission of Final Printed Carton and Container Labels for Approved NDA	Submission to NDA

EXHIBIT 10

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent No. 6,068,832
Issued:	May 30, 2000
Applicants:	Julianne Berry; Joel A. Sequeira; Imtiaz A. Chaudry
For:	CHLOROFLUOROCARBON-FREE MOMETASONE FUROATE AEROSOL FORMULATIONS

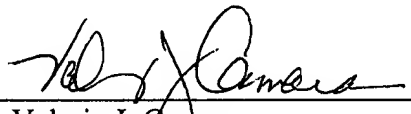
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY

In connection with the above-identified application, the undersigned attorney and/or agent hereby appoints Barry H. Jacobsen, Registration No. 43,689, c/o MERCK, Patent Department, K-6-1-1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033, an associate attorney and/or agent, to prosecute this application, to make alterations and amendments therein, to receive the patent and to transact all business in the Patent and Trademark Office connected therewith.

All communications in connection with the prosecution of the above-identified application should be sent to Barry H. Jacobsen, Registration No. 43,689, c/o MERCK, Patent Department, K-6-1-1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033.

Respectfully submitted,



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